Ring A Modification of Miltirone: Synthesis of Nitrogen Containing Compounds

by

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Last but not least, I would like to thank all my friends for their support and valuable discussion of this project.

June, 1990

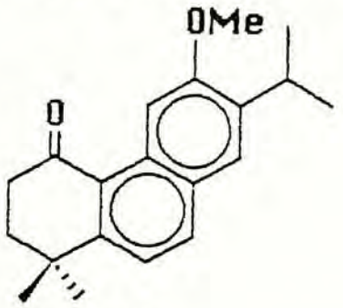
Yee-Kwan Lau

Department of Chemistry

The Chinese University of Hong Kong

II. List of Nomenclature:

1,2,3,4-Tetrahydro-1,1-dimethyl-6-methoxy-7-isopropyl-phenathren-4-one (*11*)



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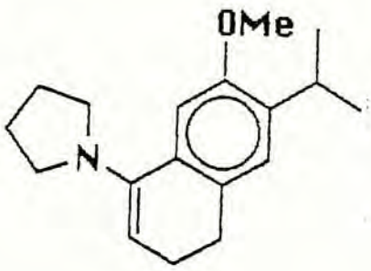

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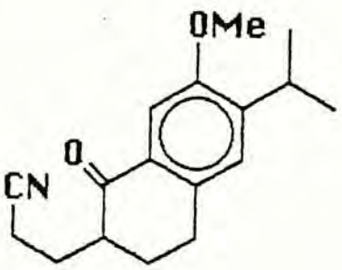

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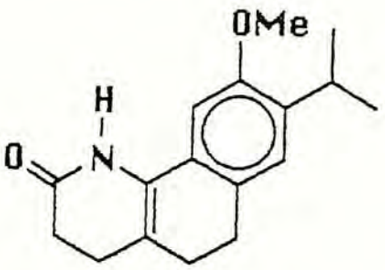

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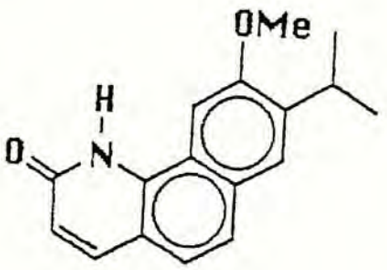

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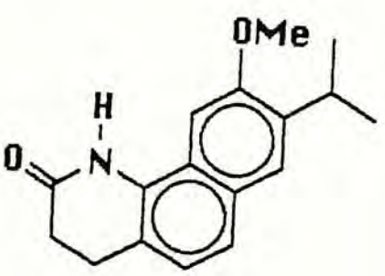

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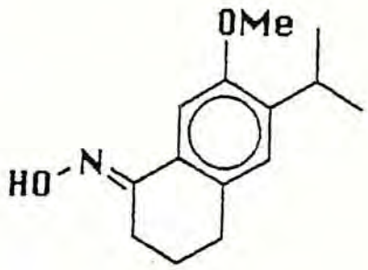
6-Isopropyl-7-methoxy-3,4-dihydro-1 (2*H*) naphthalenone oxime (*17*)



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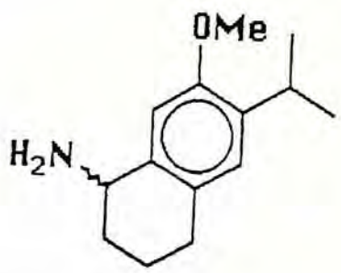

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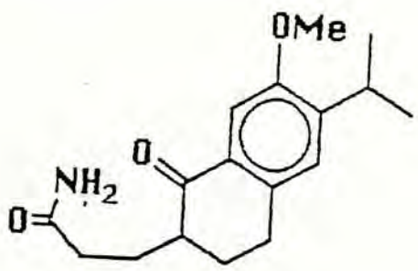
2-(6-Isopropyl-7-methoxy-3,4-dihydro-1-(2 *H*)-naphthyl)-3-propylamide (*21*)



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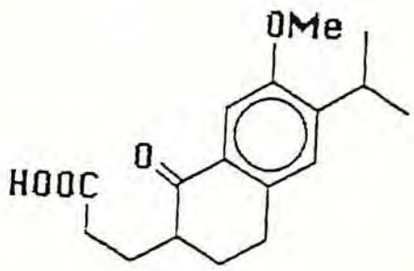
2-(6-Isopropyl-7-methoxy-3,4-dihydro-1-(2 *H*)-naphthyl)-3-propanoic acid (*22*)



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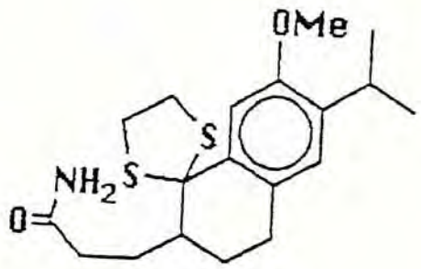
Thio-ketal of 2-(6-Isopropyl-7-methoxy-3,4-dihydro-1-(2*H*)-naphthyl)-3-propylamide (*23*)



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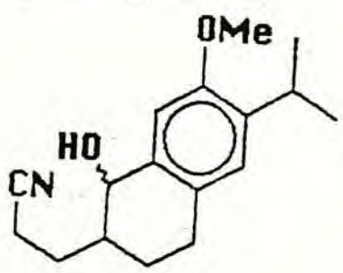
2-Cyanoethyl-6-isopropyl-7-methoxy-1,2,3,4-tetrahydro-1-naphthol (*24*)



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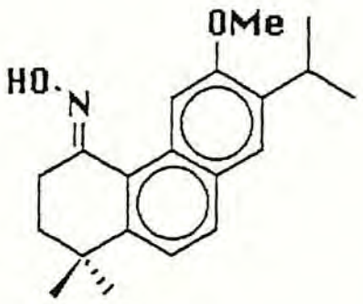
1,2,3,4-Tetrahydro-1,1-dimethyl-6-methoxy-7-isopropyl-phenanthren-4-one oxime (*27*)



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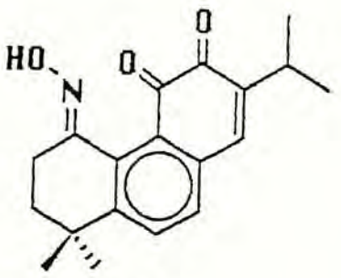
1,2,3,4-Tetrahydro-1,1-dimethyl-5,6-dioxo-7-isopropyl-phenanthren-4-one oxime (*29*)



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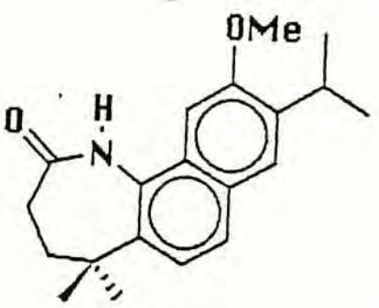
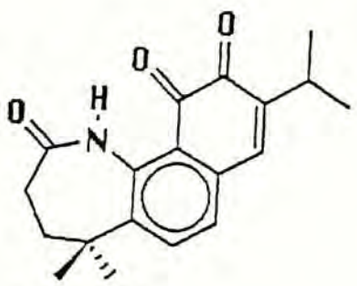
2,3,4,5-Tetrahydro-9-isopropyl-10-methoxy-naphtho [6,5-*f*] azepin-2-one (*30*)



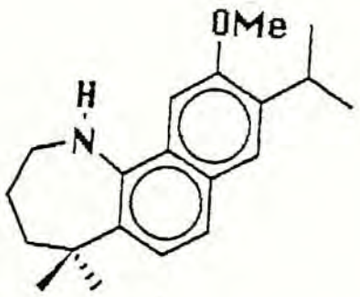
(30)

2,3,4,5-Tetrahydro-9-isopropyl-naphtho [6,5-*f*] azepin-2,10,11-trione (*32*)



(32)

2,3,4,5-Tetrahydro-9-isopropyl-10-methoxy-naphtho [6,5-*f*] azepine (*33*)



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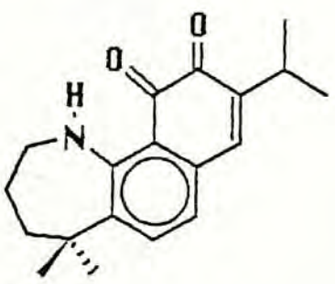
2,3,4,5-Tetrahydro-9-isopropyl-10-methoxy-naphtho [6,5-*f*] azepine-10,11-dione (*35*)



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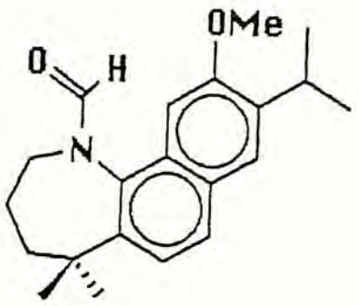
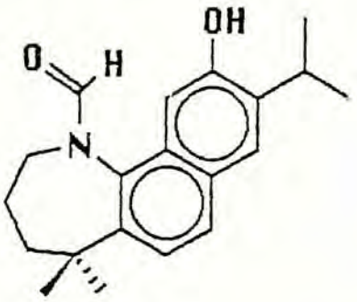
N-Formyl-2,3,4,5-tetrahydro-9-isopropyl-10-methoxy-naphtho [6,5-*f*] azepine (*39*)



(39)

N-Formyl-2,3,4,5-tetrahydro-9-isopropyl-10-methoxy-naphtho [6,5-*f*] azepin-10-ol (*40*)



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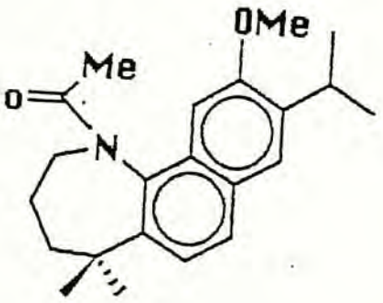
N-Acetyl-2,3,4,5-tetrahydro-9-isopropyl-10-methoxy-naphtho [6,5-*f*] azepine (*42*)



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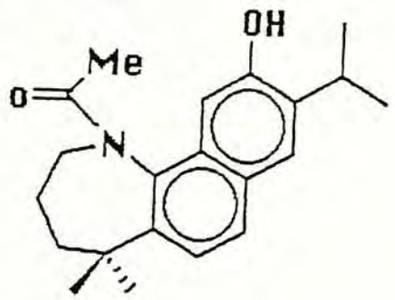
N-Acetyl-2,3,4,5-tetrahydro-9-isopropyl-10-methoxy-naphtho [6,5-*f*] azepin-10-ol (*43*)



(43)

III. Abstract

Miltirone (*I*), a component of Danshen, shows good IC_{50} value in the control benzodiazepine receptors binding assay. In addition, it possesses similar pharmacological properties as benzodiazepine including anxiolytic and anticonvulsant effects. With an aim to develop a new generation of anxiolytic drugs without the adverse effects of benzodiazepine, we have modified miltirone based on the molecular framework of benzodiazepine by incorporating a nitrogen heterocycle in the A ring of miltirone.

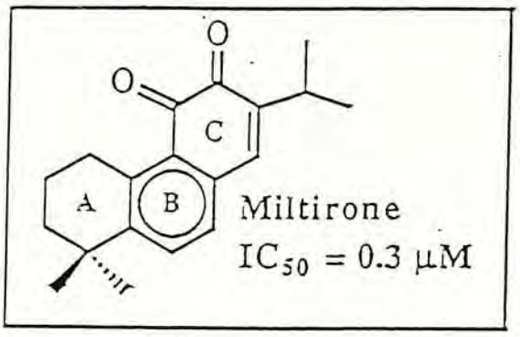
IV. Introduction:

The crude extract of *Salvia miltiorrhiza* Bunge (Danshen) has shown significant inhibition of [^{3}H]-flunitrazepam binding to central benzodiazepine receptors. In order to determine the effective components of Danshen, we have initiated a systematic isolation of tanshinones from Danshen and evaluated their tranquilizing profile at the molecular level. [1] Among all the compounds isolated, [1] a known compound, namely miltirone (***1***) [2] has shown the best IC_{50} value (0.3μM) in the central benzodiazepine receptors binding assay. Furthermore, GABA shift experiment showed that it was a partial agonist. Toxicity studies in chronic treatment manner showed that it has neither sedative nor addictive effects in mice. [3] In light of the above discoveries, we have undertaken a research program with the aim to modify miltirone (***1***) so that it can become an agonist having higher bioactivity and lower toxicity in comparison with benzodiazepines. A systematic modification of the A, B and C rings of miltirone (***1***) has been carried out [4] so that we can explore its structure-activity relationship (SAR). Consequently, the SAR study of miltirone (***1***) and its derivatives (Fig. 1) leads to the following conclusions:

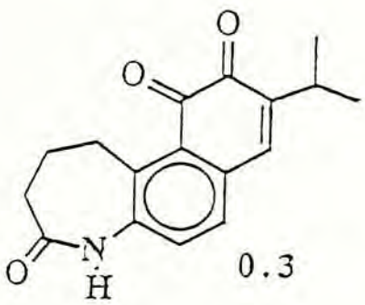
Fig.1

SAR studies of miltirone (*1*)

(The A, B and C rings modification of miltirone)



A Ring Modification



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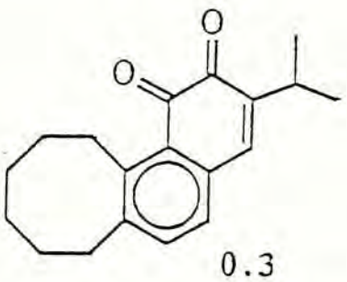

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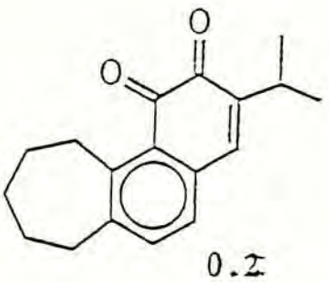

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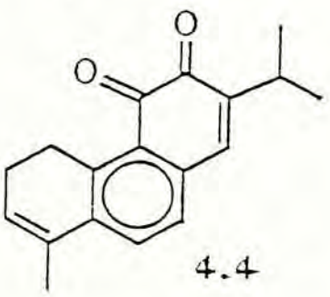

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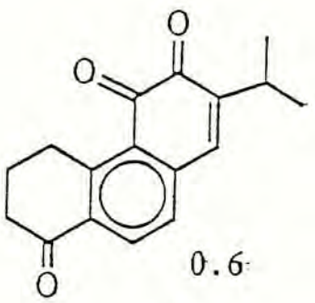

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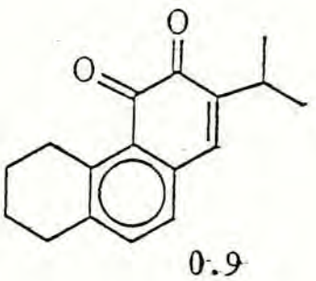

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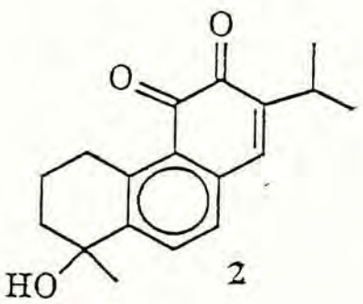

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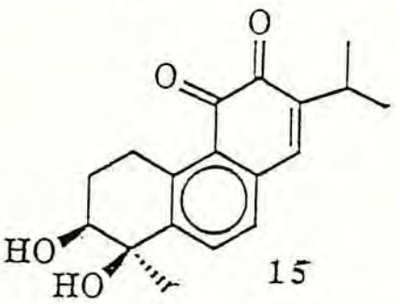

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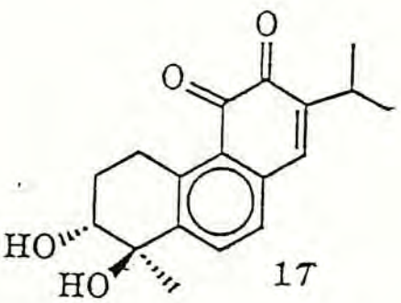

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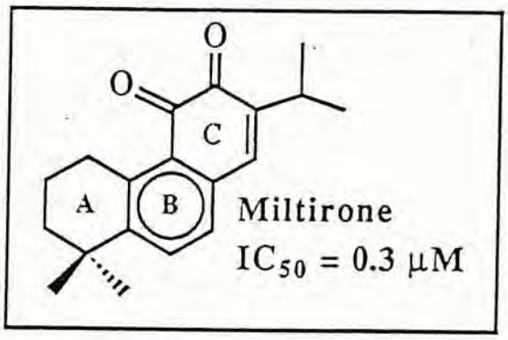
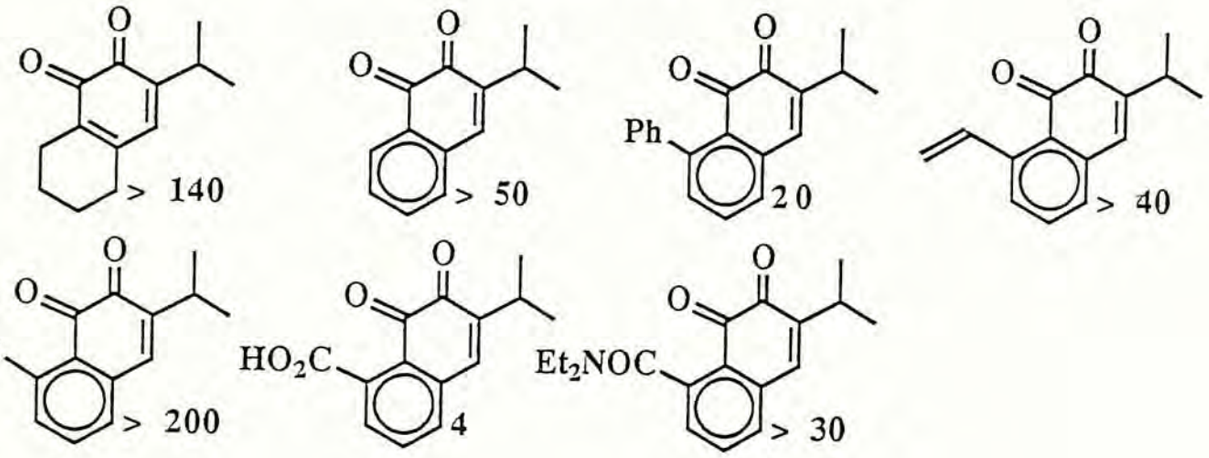
Fig.1

SAR studies of miltirone (*1*)

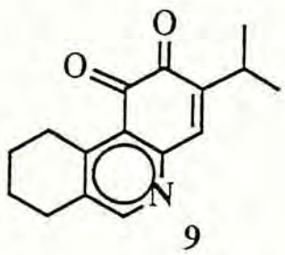
(The A, B and C rings modification of miltirone)

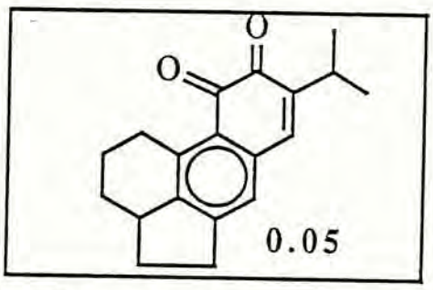


B Ring Modification in the Absence of A Ring

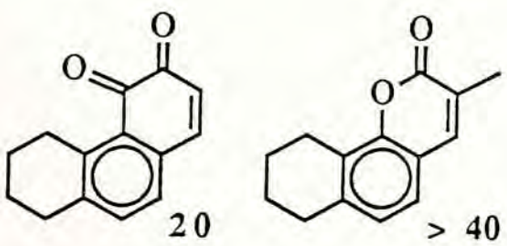


A & B Ring Modification

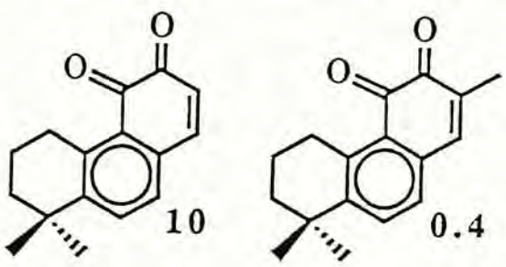




A & C Ring Modification



C Ring Modification



1. Ring A:

a) The integrity of ring A is important as activity-potency drops by a hundred-fold when ring A is absent.

b) A planar aromatic ring A reduces potency markedly.

c) The presence of a double bond in ring A, whether exocyclic or endocyclic, only reduces potency slightly.

d) Changing the size of ring A from 6 to 8-membered ring does not alter the potency to a large extent.

e) Introduction of a 4th ring system to connect ring A and B increases potency by ten fold.

2. Ring B:

a) The integrity of benzene ring is important.

3. Ring C:

a) Quinone function is important for its activity, phenol and anisole derivatives display marked reduction in potency.

b) Isopropyl side chain is also important:

(1) Restraining the free rotation of the isopropyl side chain decreases potency.

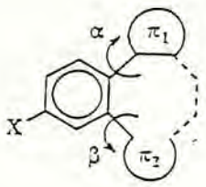
(2) Deletion of the isopropyl group leads to a twenty to a hundred-fold decrease in potency.

Based on the above observations in the SAR studies of miltirone (*1*) (Fig.1) , we would like to find out whether molecules having structures related to both miltirone (*1*) and diazepam (*2*) possess improving bioactivites. [5] After careful consideration, we reasoned that the similarity in pharmacological effects of miltirone (*1*) and diazepam (*2*) was due to their structural likeness. According to the model proposed by Fryer (Fig. 2) [6], ligands that interact at the benzodiazepine receptors complex should have the following characteristics:

Fig.2

Initial model for ligand - receptor binding. Examples of benzodiazepine and nonbenzodiazepines that interact at the benzodiazepine receptor complex.

Fryer.R.I. In *The Benzodiazepines: From Molecular Biology to Clinical Practice*; Costa.E., Ed.; Raven Press: New York, 1983; pp.7-20.



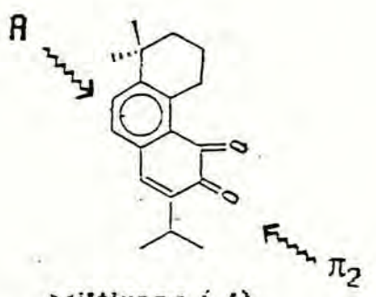
A = aromatic or heteroaromatic ring

X = electron-withdrawing group

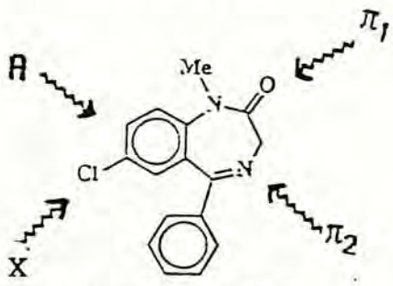
π_1 = -N-CO- group or heteroaromatic ring

π_2 = carbonyl, phenyl, or heteroaromatic ring

α, β should be in the range of 30-45°



Miltirone (*1*)

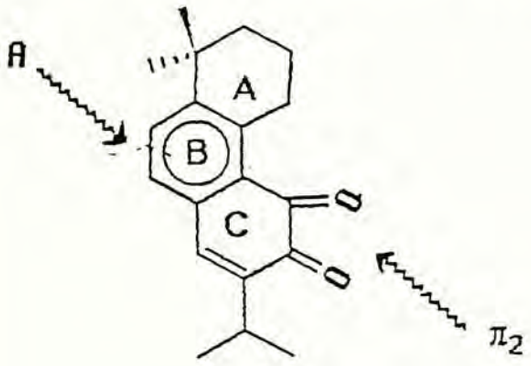


Diazepam (*2*)

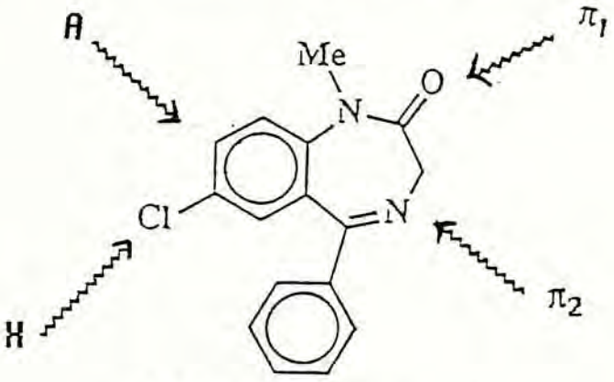
As we can see from Fig.2, miltirone (*1*) fulfills the requirement by having an aromatic ring and a π_2 system. However, it lacks the π_1 system as well as an electron-withdrawing group on the aromatic ring (Fig. 3). Therefore, we predict that the activity of miltirone (*1*) is less than that of diazepam (*2*).

The prediction is correct as we found that the IC_{50} of miltirone (*1*) was 0.3μM while that of diazepam (*2*) was 0.012 μM. (Fig.3)

Fig 3. Comparison between Miltirone (*1*) and Diazepam (*2*)



Miltirone (*1*)
IC_{50} = 0.3 μM



Diazepam (*2*)
IC_{50} = 0.012 μM

In light of this fact, we believe that the activity of miltirone (*1*) can be improved by:

a) introducing a π_1 amide system on the A ring of miltirone, or

b) introducing a nitrogen heterocycle on the A ring of miltirone, or

c) introducing an electron-withdrawing group on the B ring of miltirone.

The modifications involving the introduction of a nitrogen heterocycle and a π_1 amide system on the ring A of miltirone (*1*) are reported here and the modification by introducing an electron-withdrawing group on the B ring of miltirone will be reported elsewhere.[7]

V. Results and discussion:

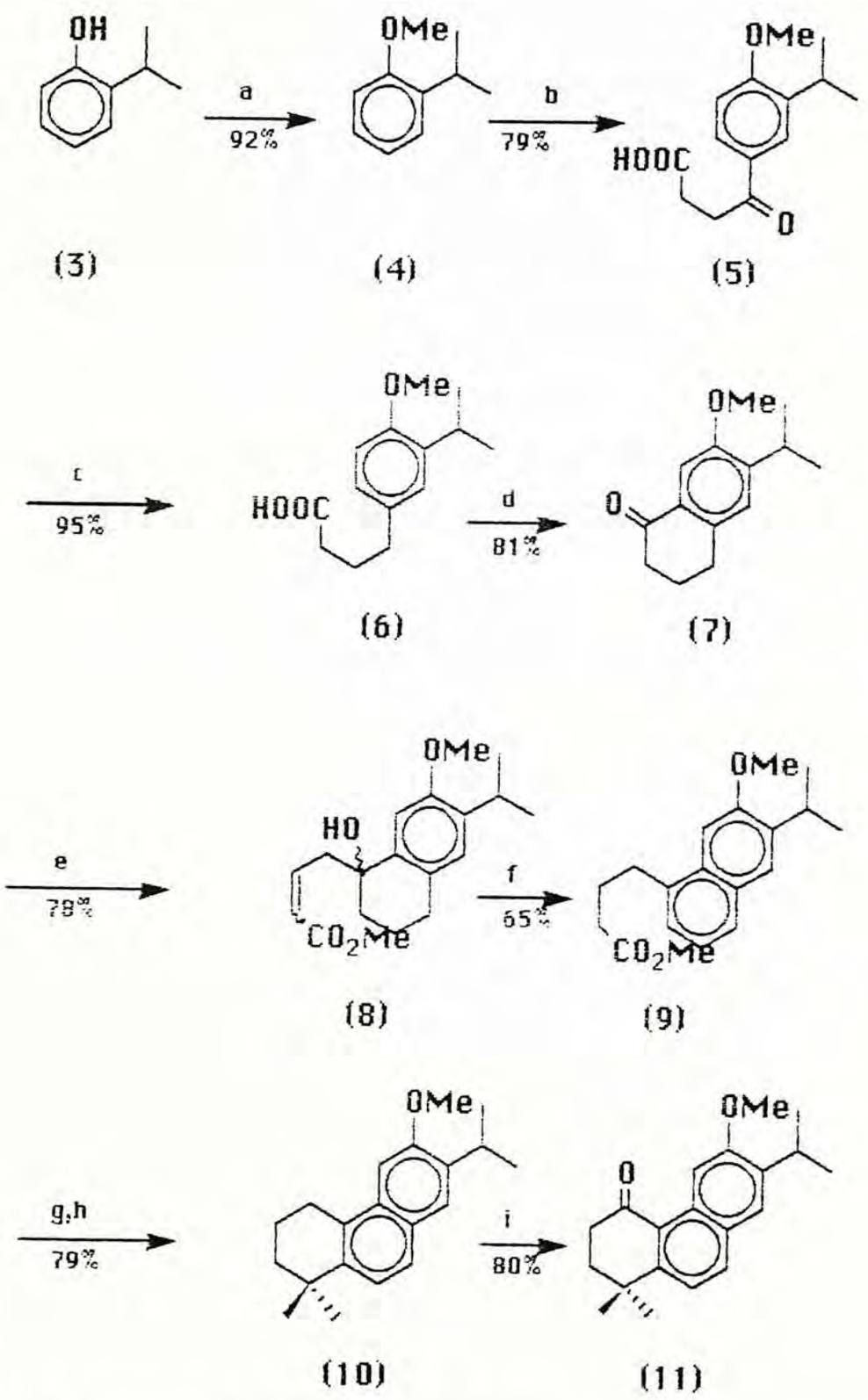
I. Synthesis of ortho-quinonoid compounds related to miltirone (*1*)

In our attempts to synthesize the nitrogen or π_1-amide containing compounds, ketone *7*, ketone *11* [1,4] and keto-nitrile *13* were three important starting materials to begin with. The preparation of these compounds were shown in Scheme 1 and 2.

Compound *7* could be obtained from the orthoisopropyl phenol *3* in four steps. Compound *3* was methylated and was followed by Friedel-Crafts acylation, Clemmensen reduction and cyclization by polyphosphoric acid (PPA) to give the tetralone *7*. (Scheme 1) [1]

In the same scheme, Compound *11* could be obtained by the Reformatsky reaction of *7* promoted by ultrasound [8,9] following by aromatization reaction to give the ester *9*. The ester *9* then underwent Grignard reaction and cyclization reaction to give compound *10*. Finally, compound *11* could be obtained through the benzylic oxidation of *10* using pyridinium chlorochromate (PCC). (Scheme 1) [1]

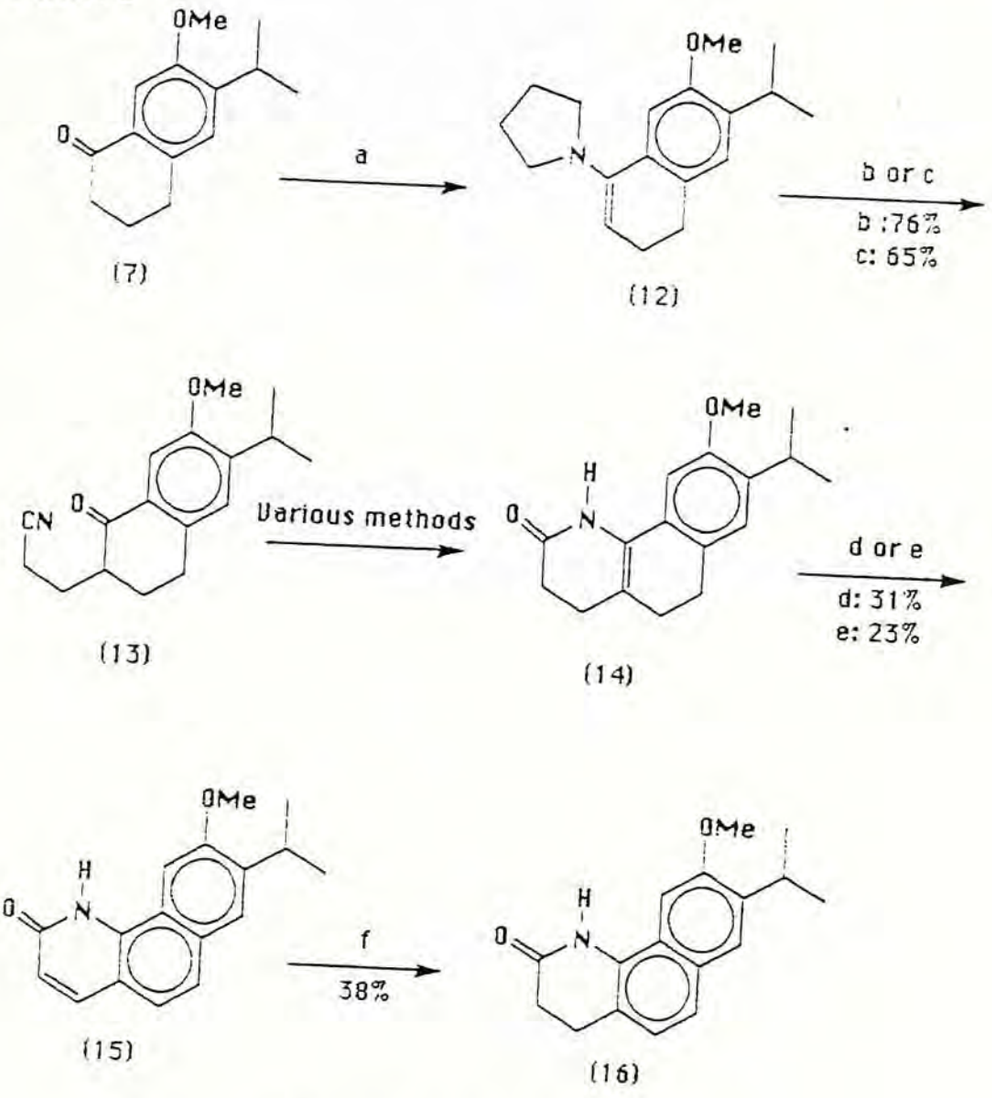
Scheme 1



a. Me_2SO_4, aq. NaOH; b. $(CH_2CO)_2O$, $AlCl_3$, CH_2Cl_2;
c. Zn, $HgCl_2$, HCl, heat; d. PPA, heat;
e. Zn, $BrCH_2CH{=}CHCO_2Me$, THF, ultrasound; f. Pd-C, 280-300°C
g. MeMgI, Et_2O; h. PPA, heat; i. PCC, CH_2Cl_2

To synthesize compound ***13***, we made use of a well developed enamine monoalkylation method developed by Stork.[10,11] Compound ***7*** was converted to the corresponding enamine ***12*** which underwent cyano-ethylation reaction to provide ***13***. (Scheme 2)

Scheme 2



a. Pyrrolidine, benzene, pTsOH, reflux
b. acrylonitrile, EtOH, reflux
c. acrylonitrile, dioxane, reflux
d. DDQ, benzene
e. Pd/C, 270-280°C
f. H_2, Pd/C

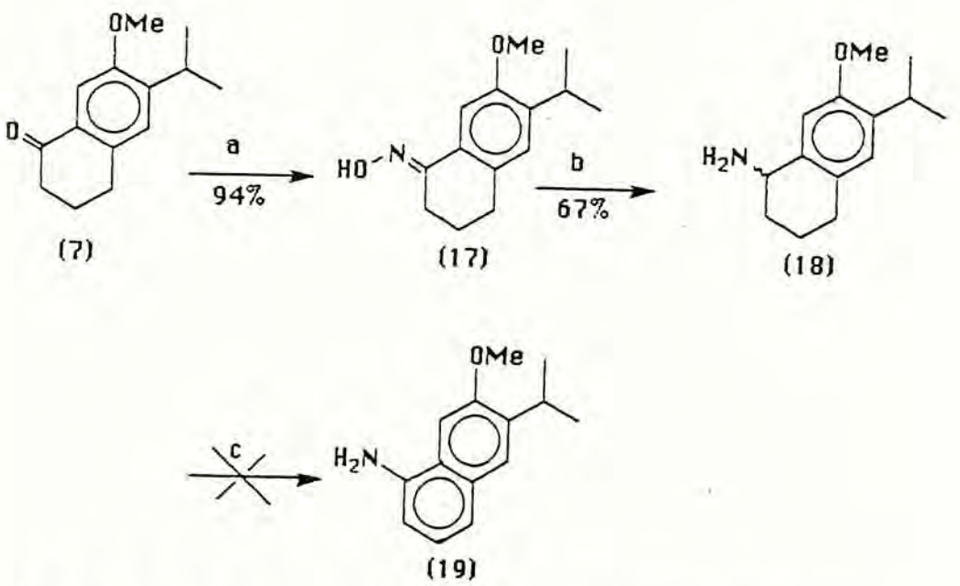
Having prepared the above three key starting materials, we then set off to modify miltirone (***1***).

A. Modification of B Ring in the absence of A Ring

In Scheme 3, three methods have been used in order to obtain a compound having an amine or an amide group on the aromatic B ring. Compound ***17*** and ***18*** were easily prepared from ***7***. However, the aromatization of them to the corresponding amine ***19*** (Scheme 3) and amide ***20*** (Scheme 4) was unsuccessful.

In Scheme 3, we have tried to aromatize the amine ***18*** with either DDQ [12] in refluxing benzene or with palladium on charcoal at 270-280°C. [1] However, both methods did not yield our desired aromatized product. Only a small amount of the amine starting material could be recovered.

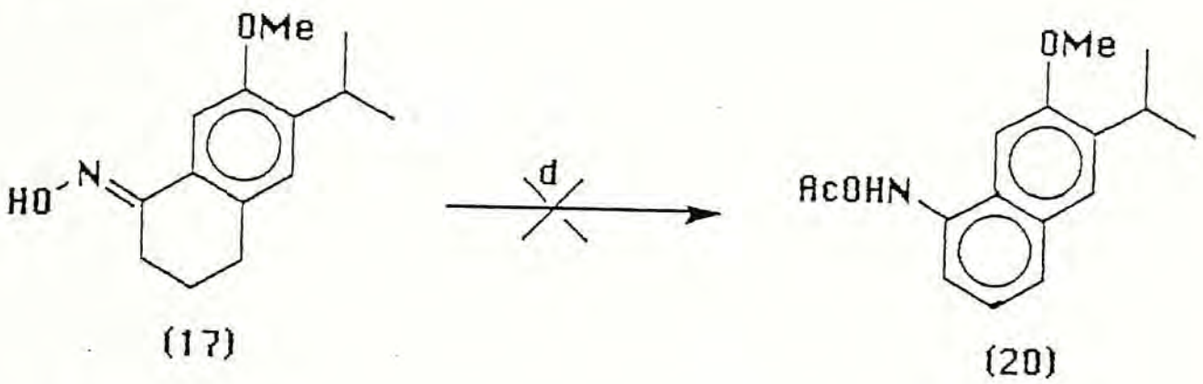
Scheme 3



a. NH_2OH. HCl, pyridine, EtOH; b. LAH, THF, reflux; c. DDQ, benzene or Pd/C, 270-280°C

For the oxidative aromatization reaction of the oxime *17* to the corresponding amide *20*, anhydrous phosphoric acid and acetic acid were employed.[13] However, the reaction was unsuccessful and only a small amount of the starting material was recovered. (Scheme 4)

Scheme 4



(17) (20)

d. H_3PO_4, HOAc, heat

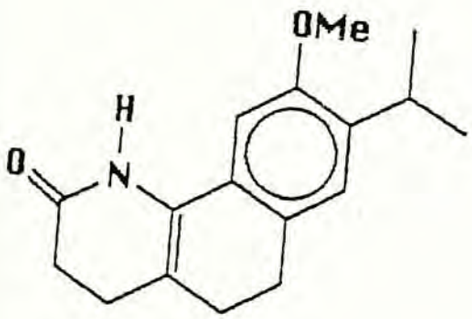
B. Attempts in the cyclization of A ring from compound *13*

(To synthesize miltirone derivatives without the gem-dimethyl groups on the A ring):

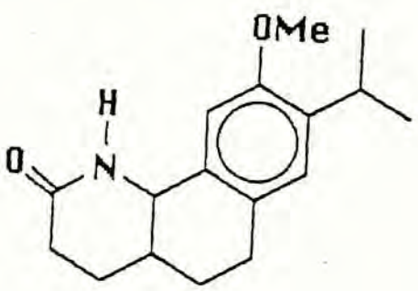
I. Acid hydrolysis methods [14,15,16,17,18]

In the attempts to obtain an amide product ***14*** or other cyclized products such as ***25*** and ***26*** from the keto-nitrile ***13***, various methods have been tried.

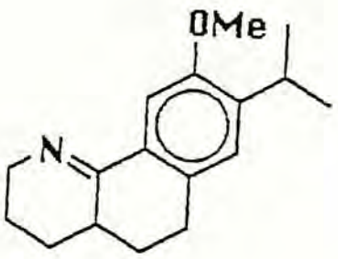
Structures of *14*, *25* and *26*



(14)



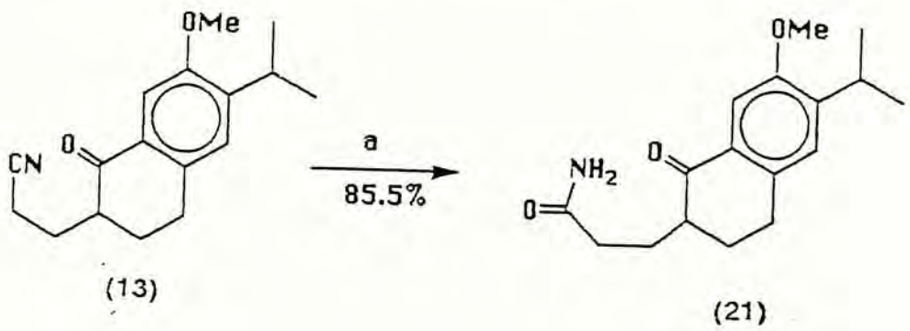
(25)

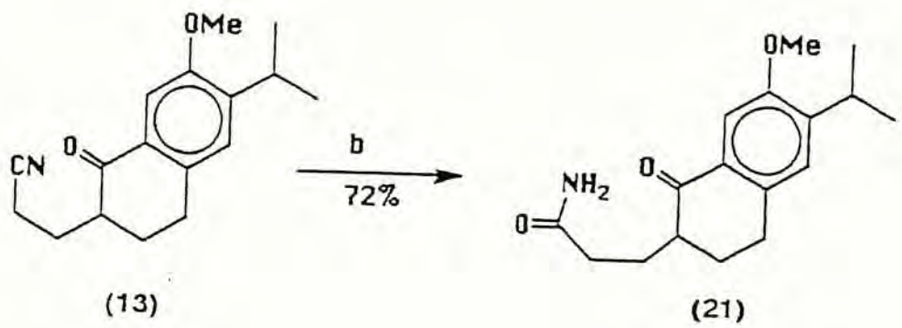


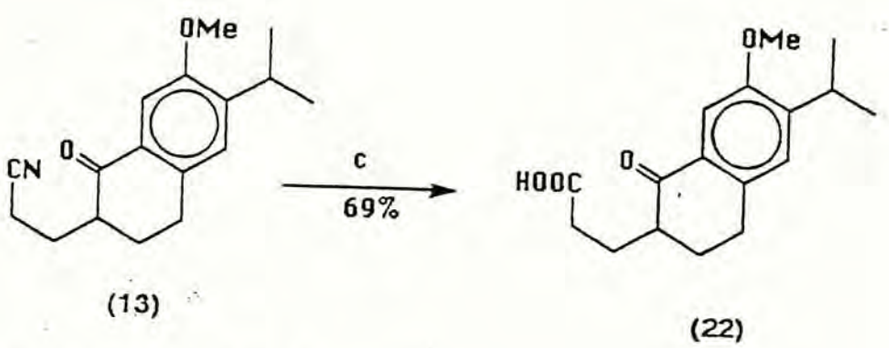
(26)

For the acid cyclization method (Scheme 5), dilute acid cannot hydrolyze the nitrile group. On the other hand, concentrated acid can hydrolyze the nitrile group but give either amide or acid product instead of the cyclized products.

Scheme 5 : Acid hydrolysis methods







a. 80% H_2SO_4, CH_2Cl_2, R.T.
b. 2M H_2SO_4, CH_2Cl_2, reflux
c. 6N H_2SO_4, CH_2Cl_2, reflux

II. Lewis acid method [19]

For the Lewis acid method, we found that boron trifluoride was a good reagent to convert the keto-nitrile ***13*** to the amide ***21***. (Scheme 6) In addition, we obtained also a small amount of the desired cyclized amide ***14*** from the reaction mixture. However, this method is disfavored due to the following drawbacks:

1) High dilution method was used and we could only handle the starting keto-nitrile ***13*** for less than 40 mg in each trial.

2) The conversion of compounds ***13*** to ***14*** is to suffer from low reproducibility as well as poor yields. (ca. 2-31%)

For this type of cyclization reaction, we have tried to use various solvent and different amount of Lewis acid. (Table1) Among which, chloroform shows the best result in yielding compound ***14***. In the consideration of the cyclization mechanism, we were not sure whether or not the proton source for the hydrolysis reaction came from the solvent. However, a control experiment showed that this reaction was able to take place in toluene which is an aprotic solvent. The mechanism of this reaction may be the same as that of the Ritter type reaction. [15] However, we have not worked out the mechanism of this reaction. It is worthy to note that the cyclization reaction using boron trifluoride is by far the best for the synthesis of amide ***14***.

Scheme 6 : Lewis acid method

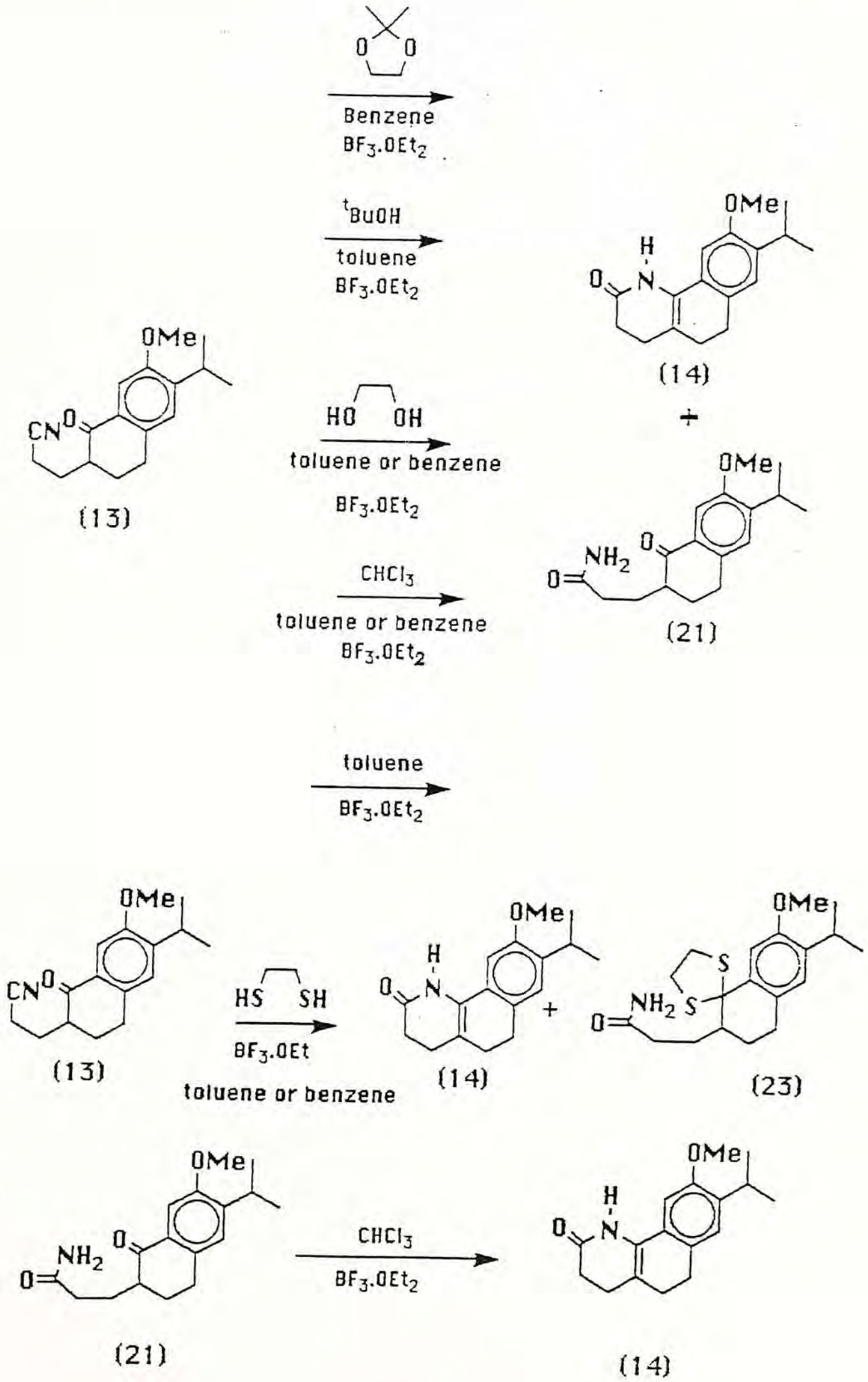
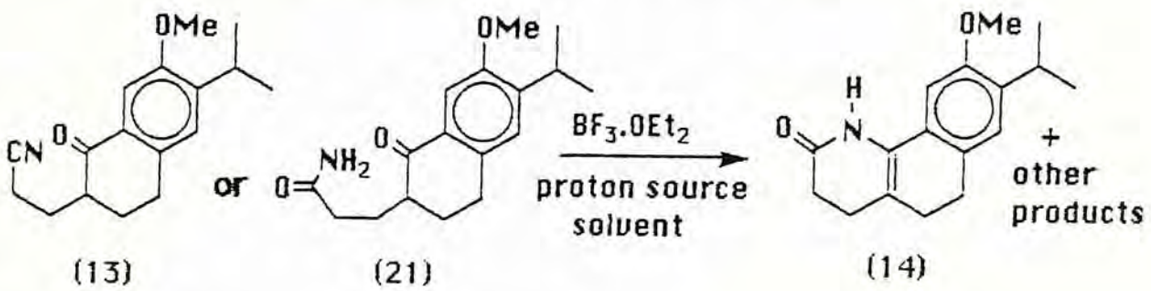
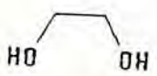
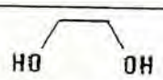


Table 1: Hydrolysis of keto-nitrile (*13*) by $BF_3.OEt_2$



(13) (21) (14)

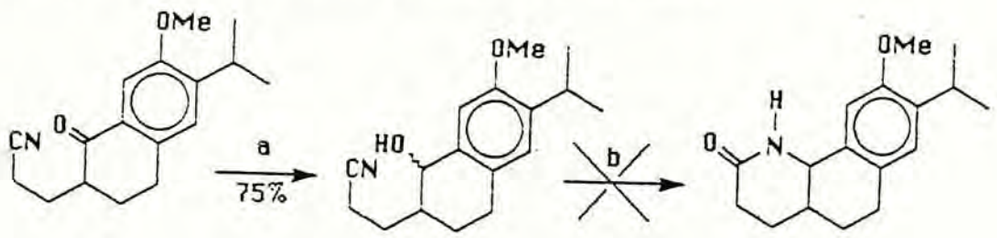
Note: '*' Refluxed with a Dean-Stark separator

Compound ~0.04g	proton source	solvent (200mL)	$BF_3.OEt_2$ (mL)	Compound / %yield
13		benzene	0.1	14/18.5% 21/19.6%
13	^tBuOH	toluene	0.1	14/12% 21/42%
13		toluene	0.1	*14/28.2% 21/63%
		benzene	0.1	*14/28% 21/51%
13		toluene	0.1	14/27% 21/58%
13		toluene	0.1	14/24% 23/59%
		benzene	0.1	14/21.5% 23/52%
13	$CHCl_3$	$CHCl_3$	0.1	14/30.2% 21/52%
			0.2	14/31.3% 21/46%
			0.4	14/24% 21/51%
13	-	toluene	0.1	14/8% 21/12%
21	$CHCl_3$	$CHCl_3$	0.2	14/12% 21/67%

III. Reductive cyclization method

For the reductive cyclization method (Scheme 7), we had tried to convert compound ***13*** to the corresponding hydroxy-nitrile ***24*** which was an ideal substrate for the Ritter reaction [15] in the production of the desired cyclized amide ***25***. However, repeated experiments applying the Ritter reaction condition [15] did not yield ***25*** as expected.

Scheme 7 : Reductive cyclization method

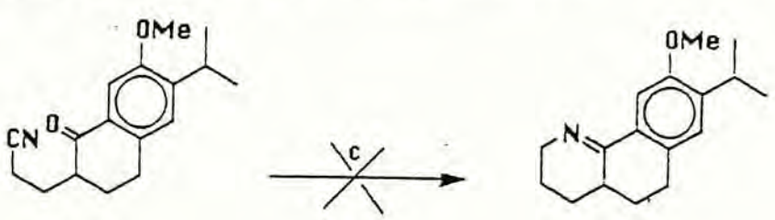


(13) (24) (25)

a. $NaBH_4$, MeOH
b. 80% H_2SO_4

In the same scheme , we have tried to cyclized compound ***13*** reductively to the corresponding imine ***26***. However, the reductive cyclization method using Raney nickel and hydrogen (50psi) [20] could not bring about any reaction.

Scheme 7 : Reductive cyclization method



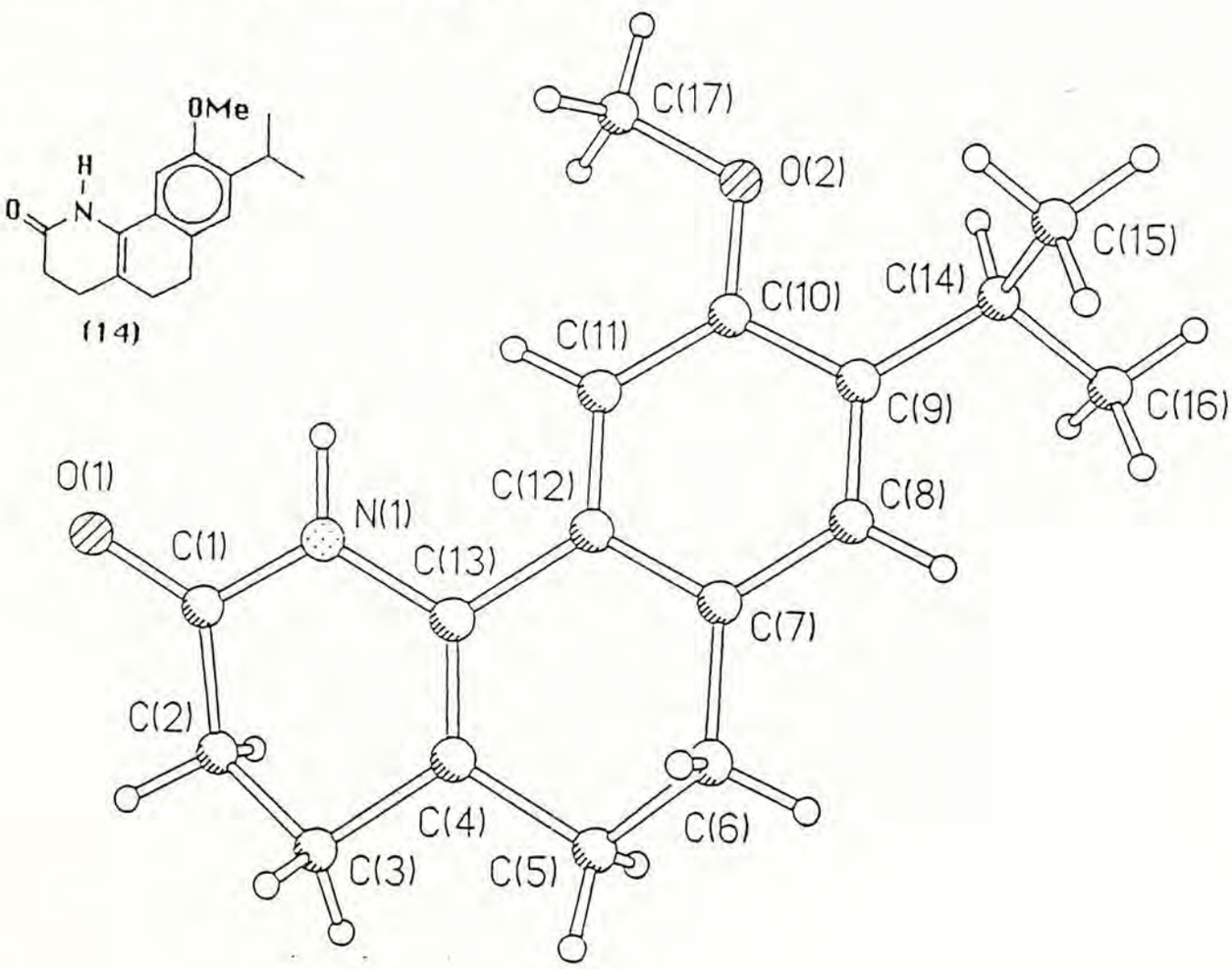
(13) (26)

c. H_2, Raney Nickel, KOH, MeOH

In the above three methods B.I, II and III, only the Lewis acid method provided the cyclized product ***14***. The structure of ***14*** was confirmed by X-ray crystallographic analysis. (Fig. 4)

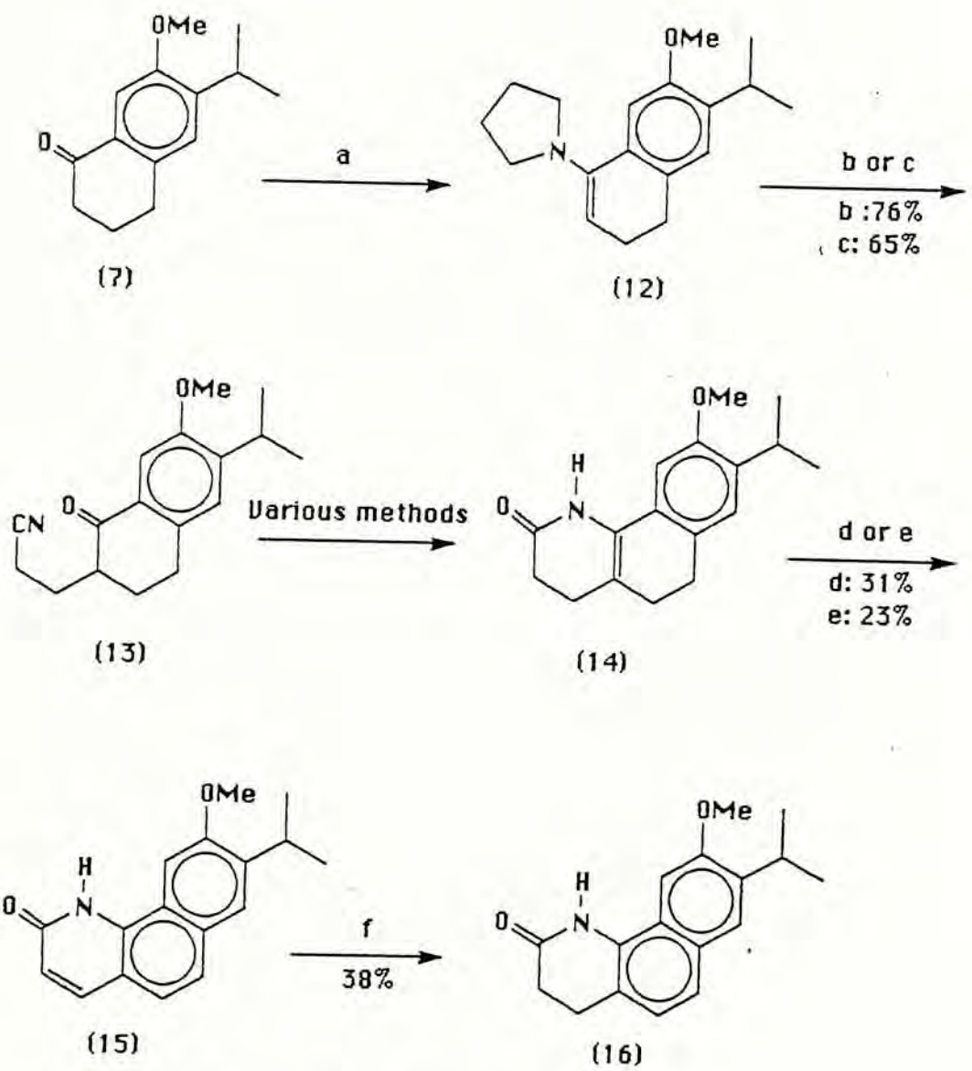
Fig.4

X-ray crystallographic study of amide *14*



After obtaining amide ***14***, we were left with the task of its aromatization. Accordingly, aromatization of amide ***14*** by either DDQ or Palladium on charcoal only gave ***15*** in poor yield. The enamide ***15*** underwent hydrogenation to give the amide ***16***. (Scheme 2) At this stage, further conversions of compound *16* into ortho-quinonoid compounds have not been attempted due mainly to the poor yields of the reactions.

Scheme 2



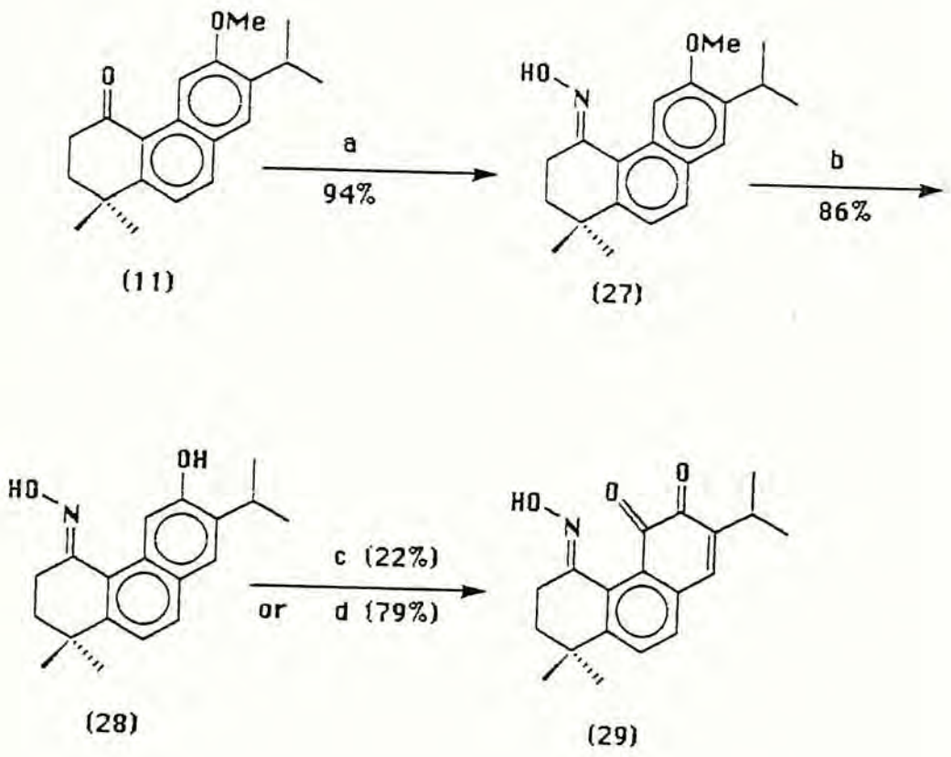
a. Pyrrolidine, benzene, pTsOH, reflux
b. acrylonitrile, EtOH, reflux
c. acrylonitrile, dioxane, reflux
d. DDQ, benzene
e. Pd/C, 270-280°C
f. H_2, Pd/C

C. Modification of the A ring of miltirone (*1*)

(Systhesis of nitrogen containing heterocycles)

As we have mentioned before, ketone ***11*** is an important starting material which can lead to the synthesis of a series of nitrogen containing compounds such as ***29*** (Scheme 8), ***32*** (Scheme 9) and ***35*** (Scheme 10 and 11).

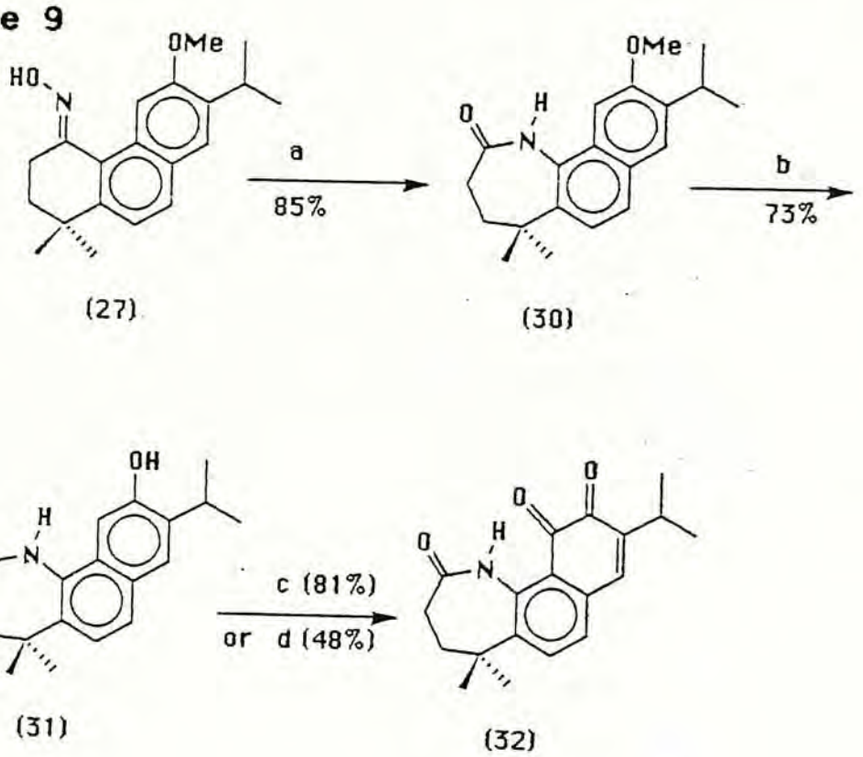
Scheme 8



a. $NH_2OH.HCl$, pyridine, EtOH; b. BBr_3, CH_2Cl_2;

c. $(KSO_3)_2NO$, KH_2PO_4, H_2O, acetone; d. $(PhSeO)_2O$, THF, heat

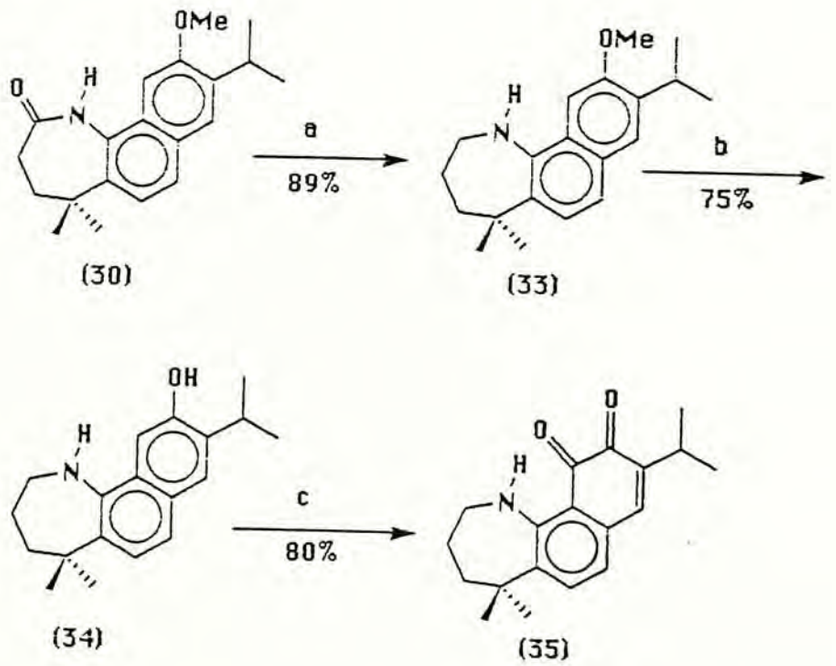
Scheme 9



a. PPA, CH_2Cl_2, 70-75 °C; b. BBr_3, CH_2Cl_2; c. $(PhSeO)_2O$, THF, heat;

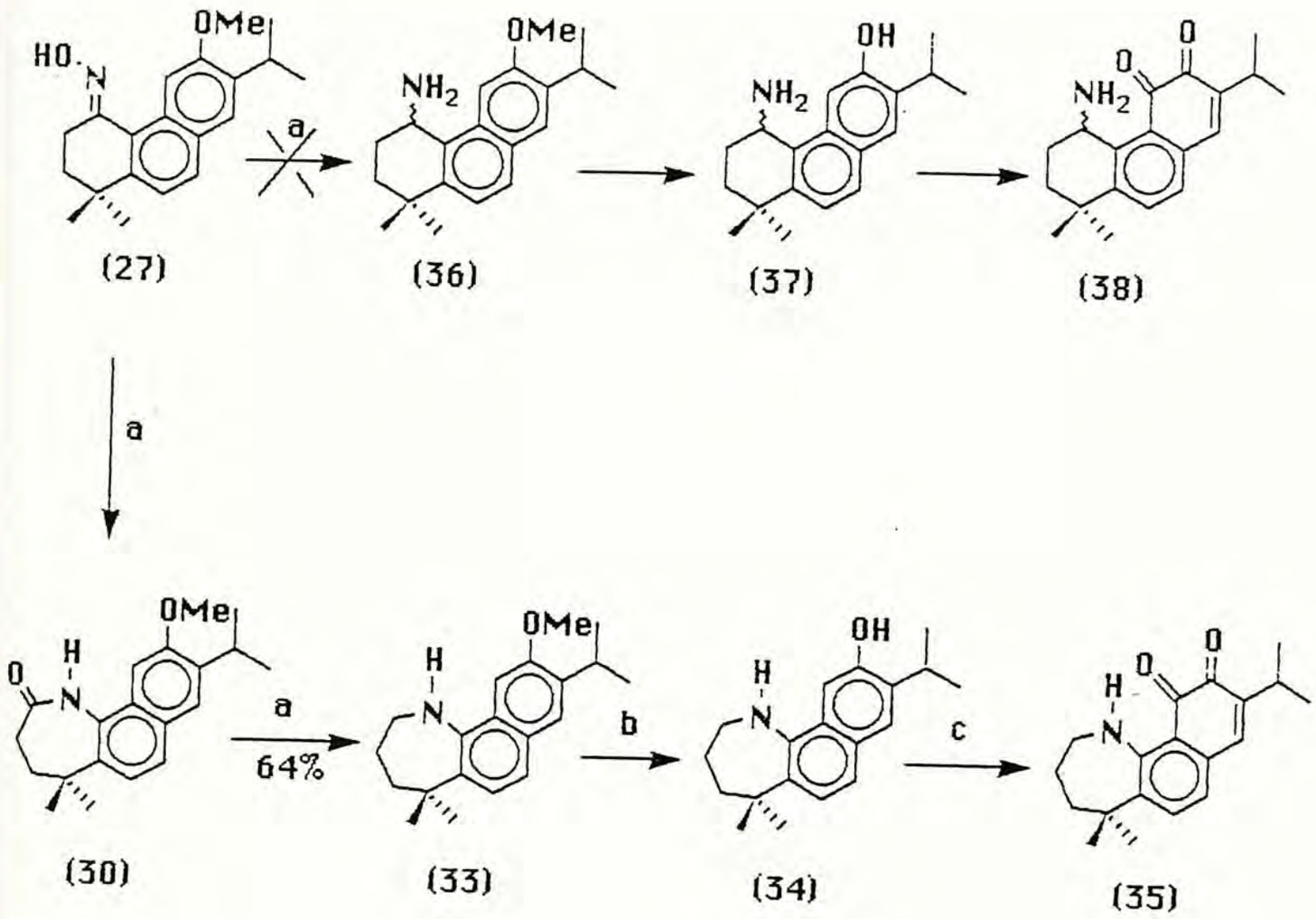
d. $(KSO_3)_2NO$, KH_2PO_4, H_2O, acetone

Scheme 10



a. $LiAlH_4$, Et_2O; b. BBr_3, CH_2Cl_2; c. $(PhSeO)_2O$, THF, heat

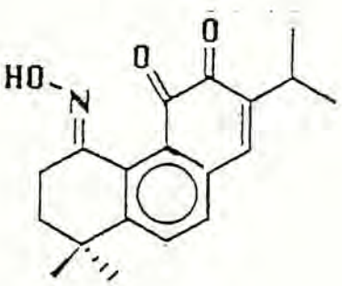
Scheme 11



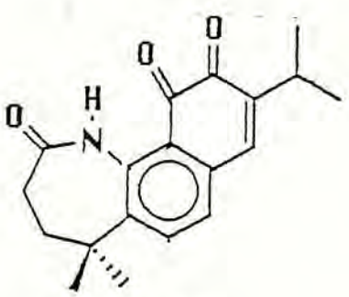
a. $LiAlH_4$, THF, reflux; b. BBr_3, CH_2Cl_2; c. $(PhSeO)_2O$, THF, heat

In Scheme 8, oxime *27* was prepared from *11*.[1] Beckmann Rearrangement [21] was employed to effect the conversion of *27* to the amide *30* (Scheme 9) which was also reduced to provide the amine *33*. (Scheme 10 and 11).[22] In Scheme 11, compound *38* with a primary amino group was our original target molecule. However, in the reduction of oxime *27*, the reaction did not proceed as predicted. We could not obtain the primary amine *36* but instead we obtained a secondary amine *33*. This reaction was perhaps due to a Beckmann Rearrangement, which was followed by a lithium aluminum hydride reduction. By using the standard transformation reactions involving demethylation and oxidation,[23,24,25] compounds *29* (Scheme 8), *32* (Scheme 9) and *35* (Scheme 10 and 11) were prepared, respectively.

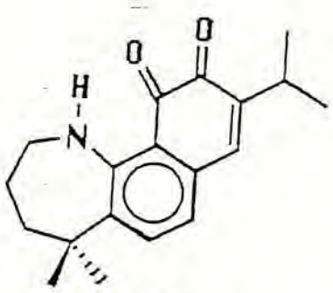
Structure of orthoquinones *29*, *32* and *35*



(*29*)



(*32*)



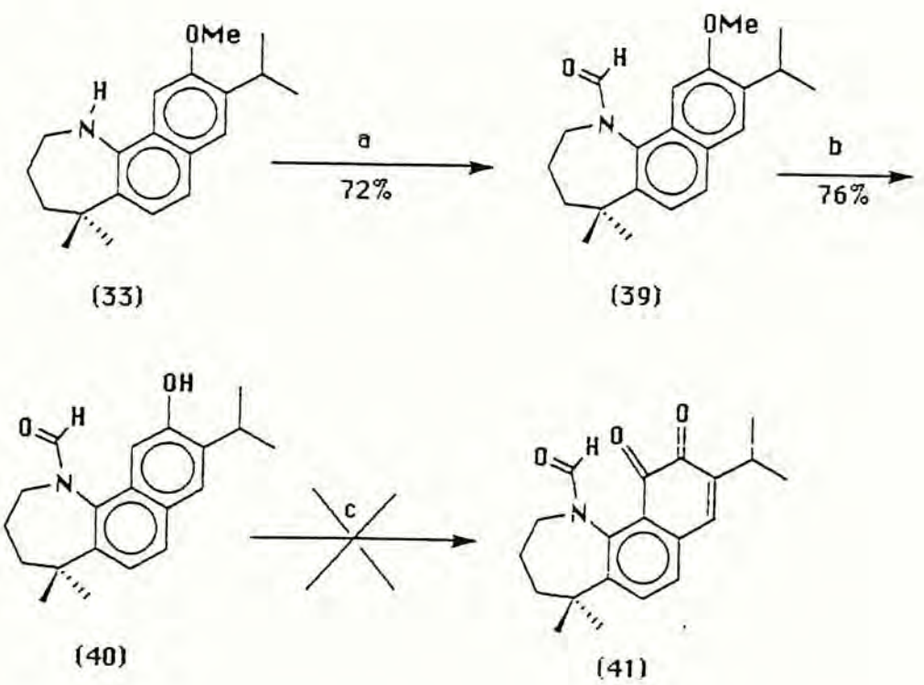
(*35*)

D. Modification of the A ring of miltirone (*1*)

(Introduction of a π_1-amide system)

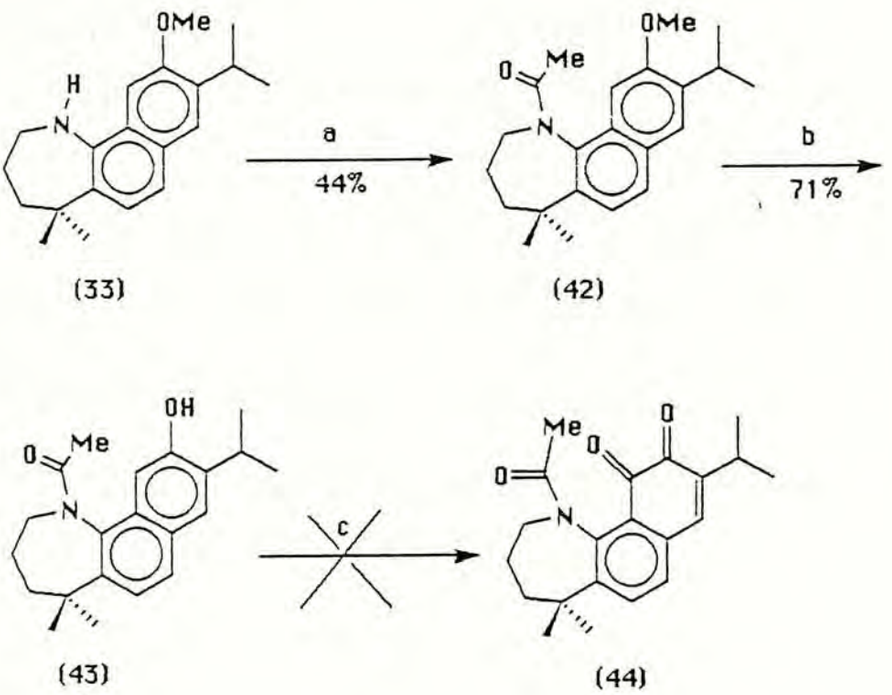
Amine ***33*** can be protected by formic acid and acetyl chloride to give the corresponding formamide ***39*** (Scheme 12) [26] and acetamide ***42*** (Scheme 13). [27,28] To obtain the desired ortho-quinonoids ***41*** and ***44***, we started from the formamide ***39*** and acetamide ***42*** by using the stardard transformation reactions. However, compound ***41*** and ***44*** were unstable and the preparation of them were unsuccessful.

Scheme 12



a. 98% HCOOH, THF, reflux; b. BBr_3, CH_2Cl_2; c. $(PhSeO)_2O$, THF, heat

Scheme 13



(33) (42)

(43) (44)

a. CH_3COCl, KOH, toluene, ultrasound; b. BBr_3, CH_2Cl_2,

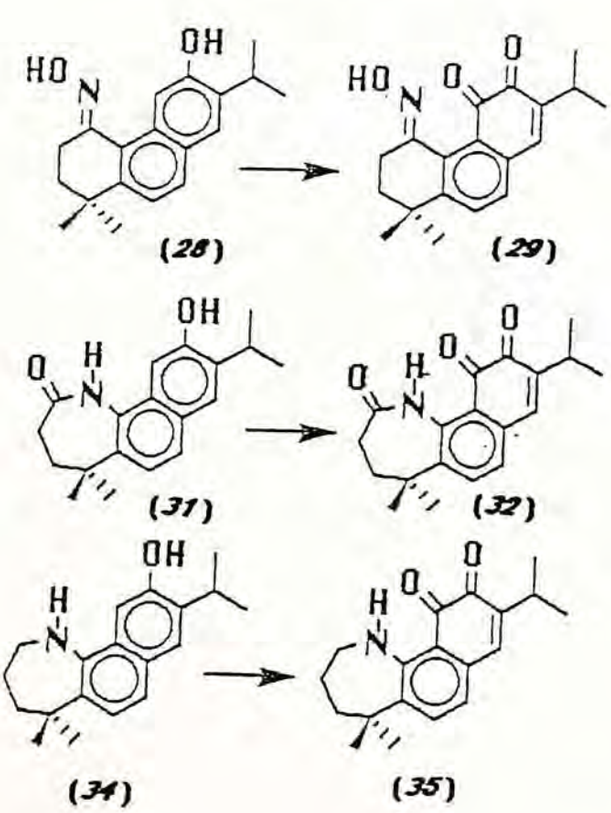
c. $(PhSeO)_2O$, THF, heat

E. Oxidation of phenol to orthoquinone

For the oxidation reaction involving the conversion of anisoles or phenols to quinones, a variety of methods have been reported. These methods include oxidative demethylation using cerium (IV) ammonium nitrate (CAN) and argentic oxide [29,30,31] in the transformation of anisole to the corresponding paraquinones. We have applied the CAN method [29] in the oxidation of a substrate whose para position is blocked and it turned out that no desired orthoquinone compound could be obtained.

In the reactions involving the oxidation of nitrogen-containing compounds, we found that benzene seleninic anhydride [24,32,33] has advantage over the Fremy's salt [25, 34] in all aspects. The oxidation using benzene seleninic anhydride is smooth and the reaction usually gave higher yield. (Fig.5) Furthermore, the solubility problem can also be overcome.

Fig.5 Comparison between Fremy's salt and benzene seleninic anhydride oxidation

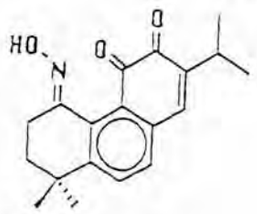
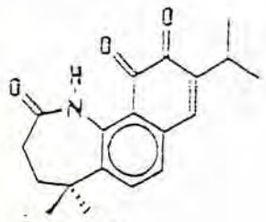
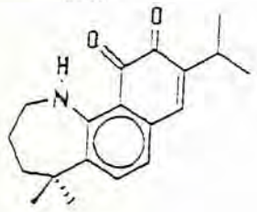
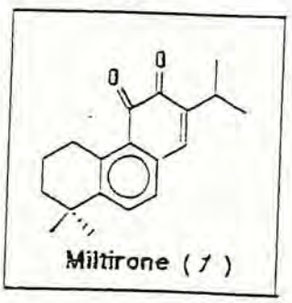


	Fremy's salt oxidation	Benzene seleninic anhydride oxidation
(28) → (29)	22%	79%
(31) → (32)	48%	81%
(34) → (35)	**unsuccessful**	80%

II. Pharmacological profile of synthetic compounds

Having successfully prepared miltirone derivatives containing a nitrogen atom or a π_1-amide system in Ring A. We then obtained the IC_{50} values of the synthetic compounds. The IC_{50} value is an indication of the binding between ligand and receptor binding site. The smaller the value, the better the fitting between the ligand and the receptor binding site. As can be seen from Table 2, only compound ***35*** showed a higher potency (ie. 0.05 μM) than the others in inhibiting the binding of [^{3}H]-flunitrazepam to central benzodiazepine receptors.

Table 2

Structure of compound	IC_{50}/μM
 (29)	1.25
 (32)	28
 (35)	0.05
 Miltirone (*1*)	0.3

Defn. of IC_{50}: Concentration of the drug which inhibits 50% of the specific binding of ^{3}H-flunitrazapam (1nm, 45 min, 0°C) to calf cerebral cortex membranes.

VI. Conclusion :

In summary, we have reported here the syntheses of three orthoquinone precursors: compound ***16***, ***40*** and ***43***, which were unable to undergo oxidation to our target molecules. Moreover, the syntheses of some modified miltirone derivatives have also been reported. Among these compounds, ***29***, ***32*** and ***35*** have a nitrogen atom attached on Ring A.

The attempts to oxidize the phenols ***40*** and ***43*** to the corresponding orthoquinones having a π_1 amide system on the A ring turned out to be unsuccessful due presumably to their instability.

Among all the orthoquinones synthesized, only compound ***35*** shows a higher bioactivity than miltirone (***1***). (IC_{50} of ***35*** is 0.05 μM and IC_{50} of ***1*** is 0.3 μM)

However, in this project, we have gained more information on the SAR of miltirone. The IC_{50} data show that the heteroatomic exo double bond on ring A can decrease the activity as can be shown by the high IC_{50} values of orthoquinones ***29*** and ***32***, which contain oxime or amide functionalities. Furthermore, we have shown that the activity can be increased by introducing an amino group to ring A (compound ***35***).

VII. Experimental Section

Solvents used were purified by standard procedures. All evaporations of organic solvents were carried out by a rotary evaporator in conjunction with a water aspirator. Proton NMR spectra were recorded on a Bruker Cryospec WM 250 (250 MHz) spectrometer or a JEOL PMX 60 SI (60 MHz) spectrometer. The chemical shifts (ppm) were measured with tetramethylsilane (TMS) serving as internal standard and deuterated chloroform was used as solvent unless stated otherwise. Mass Spectra were recorded on a VG Micromass 7070F spectrometer. Elemental analysis were carried out at Shanghai Institute of Organic Chemistry, Academia Sinica, China. Merck silica gel (60 F_{254}) precoated on aluminum sheet was used for TLC studies and Merck silica gel (70-230 mesh) was used for column chromatography unless otherwise stated. Melting points were measured on a hot-stage microscope and were uncorrected.

Methyl 2-isopropyl phenyl ether (*4*) [1]

2-Isopropyl phenol *3* (51g, 0.37mol) was mixed with 20% aqueous NaOH (200mL) and stirred vigorously for 15 min. Dimethyl sulfate (66.7g, 0.53mol) was added dropwise within one hour and the flask was immersed in an ice bath during the addition. The solution mixture was refluxed for two hours after the addition of dimethyl sulfate. Water (200mL) was added to the mixture which was followed by Et_2O extraction (3X200mL). The ethereal solution was washed with brine (2X100mL) , dried with $MgSO_4$ and evaporated. The residue was flash chromatographed on a silica gel column (eluted with hexanes) to give *4* as oil (51.8g, 92%) and the starting material *3* (1.4g) can be obtained by elution with EtOAc. MS: m/e (M^+): (calcd for $C_{10}H_{14}O$: 150) , (found: 150). ^{1}H-NMR (250MHz): δ 1.21 (d, J=6.9 Hz, 6H), 3.32 (septet, J=6.9Hz, 1H), 3.82 (s, 3H), 6.82-6.95 (m, 2H), 7.12-7.24 (m,2H).

4-Oxo-4-(3'-isopropyl-4'-methoxyphenyl) butyric acid (*5*)

Succinic anhydride (25g, 0.25mol) and sublimed $AlCl_3$ (34g, 0.25mol) were added to CH_2Cl_2 (200mL). The solution was stirred with a mechanical stirrer under nitrogen. Compound *4* (25g, 0.17mol) was added slowly and the resulting mixture was stirred for two hours at room temperature. The solution was then poured into ice-water (800mL) and 2N HCl (100mL) was added until the solution became acidic. Hexanes was added to precipitate the product. After filtration, the product obtained was dissolved in CH_2Cl_2 (200mL), dried with $MgSO_4$, evaporated and recrystallized from CH_2Cl_2 and hexanes to give colorless needles of *5* (79%). mp 133-134°C. (lit[1] mp 133-134°C) MS: m/e (M^+): (calcd for $C_{14}H_{18}O_4$: 250.1204) , (found: 250.1206). ^{1}H-NMR (250MHz): δ 1.26 (d, J=6.9 Hz, 6H), 2.80 (t, J=6.6 Hz, 2H), 3.29 (t, J=6.6 Hz, 2H), 3.31 (septet, J=6.9 Hz, 1H), 3.90 (s, 3H0, 6.87 (d, J=8.5 Hz, 1H), 7.84 (dd, J=2.1, 8.5 Hz, 1H), 7.88 (d, J=2.1 Hz, 1H).

4-(3'-Isopropyl-4'-methoxyphenyl) butyric acid (*6*)

Zinc wool (18.5g, 0.28mol), $HgCl_2$ (1.5g), conc. HCl (1.5mL) and water (40mL) were mixed together with stirring for 5 min. The aqueous layer was decanted. Compound *5* (22g, 0.09mol) in toluene (60mL) was added, followed by concentrated HCl (50mL) and water (30mL). The mixture was refluxed for 24 hours. After cooling, water (200mL) was added. The resulting mixture was extracted with CH_2Cl_2 (3X100mL), dried with Na_2SO_4

and evaporated. The residue was distilled to provide *6* (19g, 95%); bp 153-154°C (0.5mmHg) [lit [35] mp 122-123°C (benzene)]; MS: m/e (M^+): (calcd for $C_{14}H_{20}O_3$: 236) , (found:236). ^{1}H-NMR (250MHz): δ 1.2 (d, J=6.9 Hz, 6H), 1.93 (quintet, J=7.5 Hz, 2H), 2.38 (t, J=7.5 Hz, 2H), 2.61 (t, J=7.5 Hz, 2H),3.28 (septet, J=6.9 Hz, 1H), 3.80 (s, 3H), 6.76 (d, J=8.2 Hz, 1H), 6.96 (dd, J=2.2, 8.2 Hz, 1H), 7.00 (d, J=2.2 Hz, 1H).

6-Isopropyl-7-methoxy-3,4-dihydro-1(2 *H*)-naphthalenone (*7*)

Compound *6* (13.4g, 56.7mol) in CH_2Cl_2 (10mL) was added to polyphosphoric acid (120g) at 70-80°C and the resulting mixture was heated at 70-80°C for 30 min. Ice-water (100mL) was added to decompose the polyphosphoric acid and the mixture was extracted with ether (3X100mL). The ethereal extract was washed with brine (2X50mL), dried with Na_2SO_4 and evaporated. The crude product was purified by flash chromatography on a silica gel column (eluted with haxanes containing 5% EtOAc) to give light yellow oily liquid. (10g, 81%) [lit [35] bp 145-150°C (0.2mmHg)] MS: m/e (M^+): (calcd for $C_{14}H_{18}O_2$: 218) , (found:218). ^{1}H-NMR (250MHz): δ 1.19 (d, J=6.9 Hz, 6H), 2.10 (quintet, J=6.5 Hz, 2H), 2.61 (t, J=6.5 Hz, 2H), 2.89 (t, J=6.5 Hz, 2H), 3.34 (septet, J=6.9 Hz, 1H), 3.86 (s, 3H), 7.07 (s, 1H), 7.46 (s, 1H)

Methyl 4-(1,2,3,4-tetrahydro-4-hydroxy-6-isopropyl-7-methoxy-1-naphthyl) but-2-enoate (*8*) [1]

Tetralone *7* (10g, 45.9mmol), methyl 4-bromocrotonate (16.4g, 0.09 mol) and anhydrous THF was placed in a 100mL round bottom flask. Zinc dust (5.8g) was added in three portions within half an hour and the reaction mixture was allowed to react under nitrogen with the aid of an ultrasonicator for two hours. Then 2N HCl (150mL) was added and the mixture was extracted with Et_2O (3X100mL). The residue was purified by flash chromatography twice on a silica gel column (eluted with hexanes containing 14% of EtOAc) to give light yellowish oily product *8* (11g, 78%) MS: m/e (M^+): (calcd for $C_{19}H_{26}O_4$: 318) , (found: 318). ^{1}H-NMR (250MHz): δ1.17 (d, J=6.9 Hz, 3H), 1.19 (d, J=6.9 Hz, 3H), 1.73-2.09 (m, 4H), 2.63-2.79 (m, 4H), 3.25 (septet, J=6.9 Hz, 1H), 3.71 (s, 3H), 3.81 (s, 3H), 5.88 (d, J=15.7 Hz, 1H), 6.88 (s, 1H), 6.99 (s, 1H), 7.03 (dt, J=7.7, 15.7 Hz, 1H).

Methyl 4-(6-isopropyl-7-methoxy-1-naphthyl) butanoate (*9*) [1]

A mixture of the ester *8* (6g, 18.9 mmol) and 5% palladium on charcoal (340mg) was heated at 280-300°C for two hours. The mixture was then filtered through diatomaceous earth to remove the palladium black. The filtrate was evaporated and the residue was purified by flash chromatography on a silica gel column (eluted with hexanes containing 5% EtOAc) to give light yellow oily liquid *9* (3.7g, 65%). MS: m/e (M^+): (calcd for $C_{19}H_{24}O_3$: 300) , (found:300). ^{1}H-NMR (250MHz): δ 1.30 (d, J=6.9 Hz, 6H),

2.11 (quintet, J=6.5 Hz, 2H), 2.43 (t, J=6.5 Hz, 2H), 3.02 (t, J=6.5 Hz, 2H),3.42 (septet, J=6.9 Hz, 1H), 3.68 (s, 3H), 3.99 (s, 3H), 7.21-7.31 (m, 3H), 7.59-7.63 (m, 2H).

1,2,3,4-Tetrahydro-1,1-dimethyl-6-methoxy-7-isopropyl-phenathrene (*10*)

To a solution of compound *9* (3.5g, 12mmol) in anhydrous Et_2O (10mL) was added methylmagnesium iodide (5mL, 1.5M solution in Et_2O). The mixture was stirred for 3 hours and dilute HCl (100mL) was added to decompose the excess Grignard reagent. The resulting mixture was extracted with Et_2O (3X100mL). The ethereal extract was washed with brine (2X100mL) and was dried over Na_2SO_4. After evaporation, crude tertiary alcohol was obtained. The alcohol was not purified and was heated with polyphosphoric acid (50g) at 60-70°C for 30 minutes. Water (200mL) was added and the mixture was extracted with Et_2O (3X80mL). The ethereal solution was washed with brine (2X100mL), dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography on a silica gel column (eluted with hexanes) to give *10* which was recrystallized from hexanes (3g, 79%), mp 83-84°C, [lit [35] mp 83-85°C] MS: m/e (M^+): (calcd for $C_{20}H_{26}O$: 282), (found:282). ^{1}H-NMR (250MHz): δ 1.28 (d, J=6.9 Hz, 6H), 1.34 (s, 6H),1.73 (m, 2H), 1.98 (m, 2H), 3.04 (t, J=6.5 Hz, 2H), 3.40 (septet, J=6.9 Hz, 1H), 3.95 (s,3H), 7.17 (s, 1H), 7.35 (d, J=8.5 Hz,1H), 7.55 (s, 1H), 7.57 (d, J=8.5 Hz,1H)

1,2,3,4-Tetrahydro-1,1-dimethyl-6-methoxy-7-isopropyl-phenanthren-4-one (*11*)

A mixture of compound *10* (2.2g, 7.8 mmol), pyridinium chlorochromate (8.4g, 39 mmol) in CH_2Cl_2 (50mL) was stirred for 96 hours at room temperature. Then the mixture was made acidic by the addition of dilute HCl (50mL) and was extracted with CH_2Cl_2 (3X100mL). The organic extract was washed with brine (2X100mL), dried with $MgSO_4$ and evaporated. The residue was purified by flash chromatography on a silica gel column (eluted with hexanes containing 5% EtOAc) to give compound *11*, which was recrystallized from MeOH to give colorless plates (1.8g, 80%) mp 89-91°C; (lit[1] mp 89-91°C) MS: m/e (M^+): (calcd for $C_{20}H_{24}O_2$: 296) , (found:296). ^{1}H-NMR (250MHz): δ 1.29 (d, J=6.9 Hz, 6H), 1.45 (s,6H), 2.07 (t, J=6.8 Hz, 2H), 2.84 (t, J=6.8 Hz,2H), 3.40 (septet, J=6.9 Hz, 1H), 4.00 (s, 3H), 7.38 (d, J=8.6 Hz, 1H), 7.55 (s,1H), 7.80 (d, J=8.6 Hz, 1H), 8.78 (s, 1H).

3,4-Dihydro-6-isopropyl-7-methoxy-1-pyrrolidinyl-naphthalene (*12*)

Ketone *7* (4.1g, 0.02 mol) was dissolved in benzene (40mL). Then pyrrolidine (30mL) and pTsOH (0.5g) was added and the reaction mixture was refluxed under nitrogen. Dean - Stark separator was engaged to continuously remove the water produced. Removal of benzene and excess pyrrolidine provide the crude enamine *12* which was used without further purification in the next step.

2-Cyanoethyl-6-isopropyl-7-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (*13*)

Scheme 2, method b:

The crude enamine was dissolved in EtOH (50mL) followed by the addition of acrylonitrile (20mL). Then the reaction mixture was refluxed for 18 hours. Water (30mL) was added and the solution was further refluxed for an hour. The solvent was removed and 2N HCl (50mL) was added. Then the resulting solution was extracted with Et_2O (3X150mL), dried with $MgSO_4$ and evaporated. The residue was purified by column chromatography (eluted with hexanes containing 25% EtOAc) to give compound *13* as yellow solid (2.2g, reacted yield 76%) and 1.8g unreacted tetralone. Compound *13* was further purified by column chromatography and crystallization using hexanes to give colorless needles (1.5g, 68% recovery). mp 85-86°C. MS: m/e (M^+): (calcd for $C_{17}H_{21}NO_2$: 271) , (found: 271). ^{1}H-NMR (250MHz): δ 1.21 (2d, J=6.9 Hz, 6H), 1.78-2.04 (m, 2H), 2.16-2.21 (m, 2H), 2.52-2.73 (m, 3H), 2.89-3.09 (m, 2H), 3.28-3.39 (septet, J=6.9 Hz, 1H), 3.86 (s, 3H), 7.06 (s, 1H), 7.43 (s, 1H). Anal. Calcd: C, 75.23; H, 7.81; N, 5.16. Found:C, 75.31; H, 8.06; N, 4.88.

Scheme 2, method c:

The crude enamine was dissolved in dioxane (50mL) Then acrylonitrile (20mL) was added and the mixture was refluxed for 18 hours. Water (50mL) was added and the mixture was extracted with CH_2Cl_2 (3X150mL). The

organic layer was dried over $MgSO_4$, concentrated and purified by column chromatography (eluted with hexanes containing 25% EtOAc) to afford compound *13*, (1.95g, reacted yield 65%) and 2.4g unreacted tetralone. The physical and spectral data of *13* were identical with those of an authentic sample prepared previously.

8-Isopropyl-9-methoxy-3,4,5,6-tetrahydro-(1*H*)-benz [*h*] quinolin-2-one (*14*)

General procedure:

Compounds *13* or *21*, a solvent and a proton source were mixed under nitrogen according to the weight or volume stated in table 1. Then $BF_3.OEt_2$ was added by a syringe. The reaction mixture was refluxed either with or without a Dean - Stark separator at the refluxing temperature of the solvent for 24 hours. To quench the reaction, water (50mL) was added and the reaction mixture was extracted with CH_2Cl_2 and washed with saturated Na_2CO_3 (2X50mL). The organic extract was dried with $MgSO_4$, evaporated and purified by column chromatography (eluted with hexanes containing 30%EtOAc) to obtain compound *14* and other products stated.

8-Isopropyl-9-methoxy-(1 *H*)-benz [*h*] quinolin-2-one (*15*)

Scheme 2: method d: By DDQ [32]

Compound *14* (0.5g, 1.9 mmol) was dissolved in benzene (30mL). Then DDQ (0.44g, 1.94 mmole) was added and the reaction mixture was refluxed for 6 hours. Water (30mL) was added and the resulted solution was extracted with $CHCl_3$ (3X50mL). The organic extract was dried with $MgSO_4$, concentrated and purified by column chromatography (eluted by hexanes containing 50% EtOAc) to afford colorless needles *15* (0.16g, 31%) mp 248-250°C. MS: m/e (M^+): (calcd for $C_{17}H_{17}NO_2$: 267.1259) , (found:267.1256). ^{1}H-NMR (250MHz): δ 1.34 (d, J=6.9 Hz, 6H), 3.43-3.54 (septet, J=6.8 Hz, 1H), 4.22 (s, 3H), 6.72, 7.81 (2d, J=9.4 Hz, 2H), 7.39, 7.53 (2d, J=8.5 Hz, 2H), 7.67 (s, 1H), 8.24 (s, 1H).

Scheme 2, Method e: By Palladium on charcoal

Compound *14* (0.4g, 1.6 mmole), 5% palladium on charcoal (0.5g) were placed in a 25mL pear-shaped flask and heated at 270-280°C for 1.5 hours. Then $CHCl_3$ (20mL) was added to the flask and the reaction mixture was filtered through diatomatous earth. The solution was evaporated and purified by column chromatography (eluted with hexanes containing 50% EtOAc) to provide compound *15* which was further crystallized by $CHCl_3$

and hexanes to afford colorless needles (0.1g, 23%). The physical and spectral data of *17* were identical with those of an authentic sample prepared previously.

8-Isopropyl-9-methoxy-3,4-dihydro-(1 *H*)-benz [*h*] quinolin-2-one (*16*)

Compound *15* (0.16g, 0.06 mol) was dissolved in hot methanol (30mL). Then 5% palladium on charcoal (0.5g) was added and the reaction mixture was hydrogenated under hydrogen atmosphere (30psi) for 24 hours. The mixture was filtered through diatomaceous earth, evaporated and purified by column chromatography. (eluted with hexanes containing 33% EtOAc) Further purification by crystallization from hexanes - $CHCl_3$ gave colorless needles *16* (0.06g, 38%). mp 236-237°C. MS: m/e (M^+): (calcd for $C_{17}H_{19}NO_2$: 269.1416) , (found: 269). ^{1}H-NMR (250MHz): δ 1.31 (d, J=6.9 Hz, 6H), 2.76, 3.11 (q, J=7.5 Hz, 4H), 3.36-3.47 (septet, J=6.8 Hz, 1H), 4.05 (s, 3H), 7.12, 7.43 (2d, J=8.2 Hz, 2H), 7.31 (s, 1H), 7.59 (s, 1H), 9.62 (s, 1H). Anal. Calcd: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.29, H, 7.01; N, 4.95.

6-Isopropyl-7-methoxy-3,4-dihydro-1(2 *H*) naphthalenone oxime (*17*)

Compound *7* (1g, 4.9 mmol) was dissolved in EtOH (15mL), pyridine (1mL) was added, which was followed by hydroxylamine hydrochloride (0.6g, 8.6 mmol). The solution was heated at 95-100°C for 2 hours. Then 2N HCl (50 mL) was added and the solution was extracted with CH_2Cl_2 (containing 1

% MeOH) to provide the oxime *17* as colorless solid. Further purification by recrystallization of the oxime from $CHCl_3$ - hexanes gave colorless needles of 10 (1g, 94%), mp 133-134°C. [lit[1] mp 134-135°C] MS: m/e (M^+): (calcd for $C_{14}H_{19}NO_2$: 233.1416) , (found: 233.1420). ^{1}H-NMR (250MHz): δ 1.19 (d, J=6.9 Hz, 6H), 1.81 (t, J=6.0 Hz, 3H), 2.66 (t,J=5.9 Hz, 2H), 2.78 (t, J=6.5 Hz, 2H), 3.24-3.35 (septet, J=6.9 Hz, 1H), 3.82 (s, 3H), 6.96 (s, 1H), 7.39 (s, 1H). Anal. Calcd: C, 72.07; H, 8.21; N,6.01. Found: C, 72.39; H, 8.63; N, 5.96.

6-Isopropyl-7-methoxy-1,2,3,4-tetrahydro-1-napthalen-amine (*18*)

Oxime *17* (0.62g, 2.66 mmol) was dissolved in anhydrous THF (20mL). Then excess LAH (3 equivalents) was added and the reaction mixture was refluxed under nitrogen for 24 hours. Water was added dropwise to destroy the LAH and turned it into grannular filterable solid.[22] The resulting mixture was suction filtered through a bed of silica gel and washed with $CHCl_3$. Then the filtrate was concentrated and purified by column chromatography (eluted with hexanes containing 15% EtOAc) to give compound *18* which was further crystallized from $CHCl_3$ - hexanes to furnish colorless crystals (0.4g, 67%). MS: m/e (M^+): (calcd for $C_{14}H_{21}NO$: 219) , (found: 219). ^{1}H-NMR (250MHz): δ 1.18 (d, J=6.9 Hz, 6H),1.56-1.64 (m, 2H), 1.64-1.82 (m, 2H), 2.70 (t, 2H), 3.02 (t, 2H), 3.13-3.24 (septet, J=6.9 Hz, 2H), 3.75 (s, 3H), 6.25 (s, 1H), 6.89 (s, 1H). Anal. Calcd: C, 76.67; H, 9.65: N, 6.39. Found:C,76.43; H, 10.30: N, 6.03.

2-(6-Isopropyl-7-methoxy-3,4-dihydro-1-(2 *H*)-naphthyl)-3-propylamide (*21*)

Acid / Lewis acid promoted hydrolysis of keto-nitrile (*13*)

Scheme 5 a : Hydrolysis using 80% H_2SO_4

The keto-nitrile *13* (1.5g, 5.5 mmol) was dissolved in CH_2Cl_2 (5mL). Then 80% H_2SO_4 (10mL) was added and the mixture was stirred at room temperature for 2.5 hours. Ice water (50mL) was added and the solution was extracted with CH_2Cl_2 (3X100mL). The organic extract was dried with anhydrous Na_2SO_4, evaporated and purified by column chromatography (eluted with hexanes containing 50 % EtOAc) to give amide *21* (1.4g, 85%). Further purification by recrystallization of the solid from $CHCl_3$ and hexanes gave colorless sheet form crystals (1.2g, 91% recovery), mp 192-193°C. MS: m/e (M^+): (calcd for $C_{17}H_{23}NO_3$: 289.1678) , (found:289.1673). ^{1}H-NMR (250MHz): 1.20 (d, J=6.9 Hz, 6H), 1.86-2.09 (m, 2H), 2.12-2.27 (m, 2H), 2.40 (t, J=7.7 Hz, 1H), 2.49-2.62 (m,1H), 2.73-2.84 (m, 1H), 2.91-2.76 (m, 2H), 3.27-3.38 (septet, J=6.9Hz, 1H), 3.85 (s, 3H), 5.9 (d, J=4.6Hz, 2H), 7.04 (s, 1H), 7.43 (s, 1H).

Scheme 5 b: Hydrolysis using 2M H_2SO_4

The keto-nitrile *13* (0.96g, 3.54 mmole) was dissolved in CH_2Cl_2 (5mL), and was followed by the addition of 2M H_2SO_4 (45mL). The mixture was refluxed for 24 hours. After cooling, the mixture was extracted with CH_2Cl_2 (3X70mL). The organic layer was dried with anhydrous Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column (eluted with hexanes containing 50% EtOAc) to give product *21* (0.74g, 72%) as white sheet form crystals. The physical and spectral data of *21* were identical with those of an authentic sample prepared previously.

Scheme 6: Hydrolysis using Lewis acid - ($BF_3.OEt_2$)

The procedure for the preparation and the yield of compound *21* was shown in the preparation of compound *14* (vide supra)

2-(6-Isopropyl-7-methoxy-3,4-dihydro-1-(2 *H*)-naphthyl)-3-propanoic acid (*22*)

The keto-nitrile *13* (0.54g, 2 mmol) was dissolved in CH_2Cl_2 (2mL) and was followed by the addition of 6N H_2SO_4 (50mL). The resulting mixture was refluxed for 24 hours. Then it was extracted with CH_2Cl_2 (3X50mL). The organic extract was dried with $MgSO_4$, concentrated and purified by column chromatography (eluted with hexanes containing 50% EtOAc) to afford compound *22* which was further purified by crystallization from $CHCl_3$ - hexanes. (0.4g, 69%) mp 148-150°C. MS: m/e

(M^+): (calcd for $C_{17}H_{22}O_4$: 290.1518) , (found: 290.1513). ^{1}H-NMR (250MHz): δ 1.21 (d, J=6.9 Hz, 6H), 1.87 (m, 2H), 2.15-2.47 (m, 2H), 2.32-2.58 (t, J=7.6 Hz, 3H), 2.92-2.97 (dd, J=7.26 Hz, 2H), 3.27-3.38 (septet, J=6.9 Hz, 1H), 3.85 (s, 3H), 7.04 (s, 1H), 7.45 (s, 1H)

Thio-ketal of 2-(6-Isopropyl-7-methoxy-3,4-dihydro-1-(2*H*)-naphthyl)-3-propylamide (*23*)

The procedure for the preparation and the yield of compound *23* was shown in the preparation of compound *14* (vide supra) mp 174-175°C, MS: m/e (M^+) (calcd for $C_{19}H_{27}NO_2S_2$: 365.1483), (found: 365.1479). ^{1}H-NMR (250 MHz): δ 1.17 (d, J=6.9 Hz, 6H), 1.65-1.86 (m, 3H), 2.04-2.11 (m, 1H), 2.18-2.50 (m, 4H), 2.69-2.77 (m, 2H), 3.16-3.27 (septet, J= 6.9 Hz, 1H), 3.39-3.61 (m, 3H), 3.83 (s, 3H), 6.67 (s, 2H), 6.77 (s, 1H), 7.35 (s, 1H).

2-Cyanoethyl-6-isopropyl-7-methoxy-1,2,3,4-tetrahydro-1-naphthol (*24*)

The keto-nitrile *13* (1g, 3.7 mmol) was dissolved in MeOH (30mL). Then $NaBH_4$ (3 equivalents) was added and the mixture was stirred under nitrogen at 0°C for 2 hours. Water (100mL) was added and the solution was extracted with CH_2Cl_2 (3X100mL). The organic extract was dried with $MgSO_4$, evaporated and purified by column chromatography (eluted with hexanes containing 30% EtOAc) to afford the hydroxy-nitrile *24* (0.74g, 75%) mp. 94-95°C. MS: m/e (M^+): (calcd for $C_{17}H_{23}NO_2$: 273), (found:273).

^{1}H-NMR (250MHz): 1.20 (d, J=6.9 Hz, 6H), 1.43-2.13 (m, 5H), 2.45-2.59 (m, 2H), 2.66-2.79 (m, 2H), 3.22-3.33 (septet, J=6.9 Hz, 1H), 3.82 (s, 3H), 4.38 (d, J=7.4 Hz, 1H), 6.91 (s, 1H), 6.98 (s, 1H). Anal. Calcd: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.45; H, 8.59; N, 4.95.

1,2,3,4-Tetrahydro-1,1-dimethyl-6-methoxy-7-isopropyl-phenanthren-4-one oxime (*27*)

Compound *11* (1.3 g, 4.3 mmol) , Hydroxyamine hydrochoride (0.35g, 5 mmol), pyridine (0.5mL) were mixed and heated to reflux for 3 hours. Then 1N HCl (50mL) was added and the resulting solution was extracted with EtOAc (3X100mL), washed with saturated NaCl, dried with anhydrous Na_2SO_4, evaporated and purified by column chromatography (eluted with hexanes containing 20% EtOAc) to give compound *27* as colorless crystals (1.26g, 94%). mp 177-178°C. MS: m/e (M^+) (calcd for $C_{20}H_{25}NO_2$: 311.1885), (found: 311.1888). ^{1}H-NMR (250 MHz): δ 1.30 (d, J=5.8 Hz, 12H), 1.71, 2.99 (2t, J=7.02 Hz, 4H), 3.37-3.47 (septet, J=6.8 Hz, 1H), 3.98 (s, 3H), 7.34, 7.70 (2d, J=8.5 Hz, 2H), 7.57 (s, 1H), 8.23 (s, 1H). Anal. Calcd: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.69; H, 8.65; N, 4.07.

1,2,3,4-Tetrahydro-1,1-dimethyl-5,6-dioxo-7-isopropyl-phenanthren-4-one oxime (*29*)

To a stirred solution of compound *27* (0.78g, 2.5 mmol) in CH_2Cl_2 (15mL) cooled at 0°C was added boron tribromide (0.7mL) slowly via a syringe. The solution was stirred at room temperature for 1 hour. Then ice water (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3X75mL). The organic layer was dried with $MgSO_4$, evaporated and purified by column chromatography (eluted with hexanes containing 35% EtOAc) to give compound *28* (0.64g, 86%) mp 145-148°C. MS: m/e (M^+) (calcd for $C_{19}H_{23}NO_2$: 297), (found: 297). ^{1}H-NMR (250 MHz):1.12 (s, 6H), 1.24 (d, J=6.8 Hz, 6H), 1.54, 2.84 (2t, J=6.74 Hz, 4H), 3.32 (septet, J=6.8 Hz, 1H), 7.18, 7.64 (2d, J=8.6 Hz, 2H), 7.47 (s, 1H), 8.25 (s, 1H), 9.00 (s, 2H). Compound *28* was not further purified and was used directly in the next step.

Scheme 8, method c: By Fremy's salt

A solution of compound *28* (0.58g, 1.95 mmol) in acetone (15mL) was added to a solution of potassium nitroso-disulfonate (546 mg) and 0.125M aqueous potassium hydrogen phosphate (8mL) in water (25mL) with stirring. The mixture was stirred for 24 hours. Acetone was evaporated and water (40 mL) was added. The resulting solution was extracted with Et_2O (3X50

mL). The aqueous layer was allowed to stand overnight and was again extracted with Et_2O (3X50mL). The organic extract was dried with Na_2SO_4 and evaporated. The residue was purified by column chromatography (eluted with hexanes containing 20% EtOAc) to give compound *29* as orange crystals (0.13g, 22%). mp 158-159°C. MS: m/e (M^+) (calcd for $C_{19}H_{21}NO_3$: 311), (found: 311). ^{1}H-NMR (250 MHz): δ 1.66 (t, J=6.9 Hz, 6H), 1.35 (d, J=7.65 Hz, 6H), 1.93, 2.90 (2t, 4H), 3.06 (septet, J=6.8 Hz, 1H), 4.8 (s, 1H), 7.15 (s, 1H), 7.38, 7.69 (2d, J=7.2 Hz, 2H). Anal. Calcd: C, 73.29; H, 6.80; N, 4.50. Found : C, 73.97; H, 6.84; N, 4.30.

Scheme 8, method d: By Benzene Seleninic Anhydride

Compound *28* (0.84g, 2.8 mmol) was dissolved in anhydrious THF (30mL). Then benzene seleninic anhydride (0.7g) was added and the reaction mixture was heated to 50°C for 30 minutes. Saturated sodium carbonate solution (50mL) was added and the solution was extracted with CH_2Cl_2 (3X 100mL). The organic extract was dried with $MgSO_4$ and evaporated. The residue was purified by column chromatography (eluted with hexanes containing 20% EtOAc) to give compound *29* as orange solid. (0.69g, 79%) The solid was further purified by crystallization using MeOH to provide yellow crystals (0.54g, 78% of recovery). The physical and spectral data of *29* were idential with those of an authentic sample prepared previously.

2,3,4,5-Tetrahydro-9-isopropyl-10-methoxy-naphtho

[6,5-*f*]azepin-2-one (*30*)

The oxime *27* (1g, 3.4 mmol) was dissolved in CH_2Cl_2 (20mL) and was added to a mechanically stirred PPA solution (20g) dropwise at 70-75°C. The reaction was monitored by TLC. After about 30 minutes, TLC showed that all the oxime had reacted. The reaction mixture was poured into ice-water (100mL) to decompose the PPA and the mixture was extracted with Et_2O (3X150mL). The ethereal extract was dried with Na_2SO_4 and evaporated to give yellow solid. The crude product was purified by column chromatography (eluted with hexanes containing 30% EtOAc) to give 30 which was recrystallized from EtOAc - hexanes (0.9g, 85%). mp 208-210°C; MS: m/e (M^+) (calcd for $C_{20}H_{25}NO_2$: 311) (found: 311). ^{1}H-NMR (250 MHz): δ 1.30 (d, J=6.9 Hz, 6H), 1.50 (s, 6H), 2.23-2.39 (m, 4H), 3.36-3.47 (septet, J=6.8 Hz, 1H), 3.98 (s, 1H), 7.26 (s, 1H), 7.43, 7.63 (2d, J=8.2 Hz, 3H), 8.18 (s, 1H). Anal. Calcd: C, 77.14; H, 8.09; N, 4.50. Found : C, 76.68; H, 8.16, N, 4.23.

2,3,4,5-Tetrahydro-9-isopropyl-naphtho[6,5-*f*]azepin-2,10,11-trione (*32*)

To a stirred solution of compound *30* (0.6g, mmol) in CH_2Cl_2 (15mL) cooled at 0°C was added boron tribromide (0.6mL) slowly via a syringe. The solution was stirred at room temperature for 1 hour. Then ice water (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3X75mL). The organic layer was dried with $MgSO_4$, evaporated and purified by column chromatography (eluted with hexanes containing 35% EtOAc) to give compound *31* (0.4g. 73%) mp 197-199°C. MS: m/e (M^+) (calcd for $C_{19}H_{23}NO_2$: 297), (found:297). ^{1}H-NMR (250 MHz): δ 1.34 (d, J=6.8 Hz, 6H), 1.47 (s, 1H), 2.21, 2.39 (2t, J=6.35 Hz, 4H), 3.39-3.45 (septet, J=6.9 Hz, 1H), 7.26 (s, 1H), 7.37, 7.63 (2d, J=8.7 Hz, 3H). Compound *31* was not further purified and was used directly in the next step.

Scheme 9, method d: By Fremy's salt [24]

A solution of compound *31*(0.4g, 1.4 mmol) in acetone (15mL) was added to a solution of potassium nitrosodisulfonate (527 mg) and 0.125M aqueous potassium hydrogen phosphate (8mL) in water (25mL) with stirring. The mixture was stirred for 24 hours. Acetone was evaporated and water (40 mL) was added. The resulting solution was extracted with Et_2O (3X50 mL).

The aqueous layer was allowed to stand overnight and was again extracted with Et_2O (3X50mL). The organic extract was dried with Na_2SO_4 and evaporated. The residue was purified by column chromatography (eluted with hexanes containing 20% EtOAc) to give compound *32* as red crystals (0.2g, 48%). mp 172-173°C . MS: m/e (M^+) (calcd for $C_{19}H_{21}NO_3$: 311), (found: 311). ^{1}H-NMR (250 MHz):1.18 (d, J=6.86, 6H), 1.43 (s, 6H) , 2.16, 2.46 (2t, J=7.3 Hz, 4H), 2.99-3.10 (septet, J=6.75 Hz, 1H), 7.02, 7.66 (2d, J=7.9 Hz, 2H), 7.12 (s, 1H), 10.90 (s, 1H). Anal. Calcd: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.05; H, 6.67; N, 4.16.

Scheme 9, method c: By Benzene Seleninic Anhydride

Compound *31* (0.8g, 2.7 mmole) was dissolved in anhydrious THF (30mL). Then benzene seleninic anhydride (0.7g) was added and the reaction mixture was heated to 50°C for 30 minutes. Saturated sodium carbonate solution (50mL) was added and the solution was extracted with CH_2Cl_2 (3X 100mL). The organic extract was dried with $MgSO_4$ and evaporated. The residue was purified by column chromatography (eluted with hexanes containing 20% EtOAc) to give compound 32 as red crystals. (0.67g, 81%). The physical and spectral data of compound *32* were identical with those of an authentic sample.

2,3,4,5-Tetrahydro-9-isopropyl-10-methoxy-naphtho

[6,5-*f*] azepine (*33*)

Scheme 10, method a: By the reduction of compound (*30*)

A mixture of compound *30* (0.94g, 3 mmol), LAH (0.6g), Et_2O (30mL) was refluxed at 30°C under nitrogen for 24 hours. Then water was added dropwise to convert the hydride into filtrable $LiAlO_2$ grannular precipitation. The resulted mixture was suctioned filtered through a bed of silica gel (5g, 70-230 mesh) and CH_2Cl_2 was used as eluent. The filtrate was evaporated and the residue was purified by column chromatography (eluted with hexanes containing 5% hexanes) to give compound *33* (0.8g, 89%). mp 69-71°C. MS: m/e (M^+) (calcd for $C_{20}H_{27}NO$: 297.2093), (found: 297.2084). ^{1}H-NMR (250 MHz): δ 1.28 (d, 6.88 Hz, 6H), 1.45 (s, 6H), 1.54-1.74 (m, 2H), 1.87-1.95 (m, 2H), 3.19 (t, J=5.8 Hz, 2H), 3.33-3.44 (septet, J=6.9 Hz, 1H), 3.94 (s, 3H), 4.22 (s, 1H), 7.01 (s, 1H), 7.28, 7.37 (2d, J=8.7 Hz, 2H), 7.55 (s, 1H)

Scheme 11, method a: By the reduction of oxime (27)

Oxime *27* (0.7g, 2.2 mmole) was dissolved in anhydrous THF (20mL). Then excess LAH (3 equivalents) was added and the reaction mixture was refluxed under nitrogen for 24 hours. Water was added dropwise to destroy

the LAH and turned it to grannular filterable solid. The resulting mixture was suction filtered through a bed of silica gel and washed with $CHCl_3$. Then the filtrate was concentrated and purified by column chromatography (eluted with hexanes containing 15% EtOAc) to give compound *33* (0.42g, 64%) whose physical and spectral data were identical to those of an authentic sample prepared previously.

2,3,4,5-Tetrahydro-9-isopropy-naphtho[6,5- *f*] azepine-10,11-dione (*35*)

To a stirred solution of compound *33* (0.47g, 21.6 mmol) in CH_2Cl_2 (15mL) cooled at 0°C was added boron tribromide (0.7mL) slowly via a syringe. The solution was stirred at room temperature for 1 hour. Then ice water (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3X75mL). The organic layer was dried with $MgSO_4$, evaporated and purified by column chromatography (eluted with hexanes containing 35% EtOAc) to give compound 34 (0.34g, 75%). MS: m/e (M^+) (calcd for $C_{19}H_{25}NO$: 283), (found: 283). ^{1}H-NMR (250 MHz): δ 1.33 (d, J=6.9 Hz, 6H), 1.43 (s, 6H), 1.71-1.75 (m, 2H), 1.86-1.95 (m, 2H), 3.13 (t, J=5.83 Hz, 2H), 3.26-3.37 (septet, J=6.8 Hz, 1H), 3.83 (s, 3H), 7.08 (s, 1H), 7.30, 7.36 (2d, J=8.8 Hz, 2H), 7.57 (s, 1H). Compound *34* was not further purified and was used directly in the next step.

Compound *34* (0.86g, 3 mmol) was dissolved in anhydrious THF (40mL).

Then benzene seleninic anhydride (0.8g) was added and the reaction mixture was heated to 50°C for 30 minutes. Saturated sodium carbonate solution (50mL) was added and the solution was extracted with $CHCl_3$ (3X 100mL). The organic extract was dried with $MgSO_4$ and evaporated. The residue was purified by column chromatography (eluted with hexanes containing 20% EtOAc) to give compound *35* (0.7g, 80%) as purple oil. MS: m/e (M^+) (calcd for $C_{19}H_{23}NO_2$: 297.1729), (found: 297.1726). ^{1}H-NMR (250 MHz): δ 1.15 (d, J=6.82 Hz, 6H), 1.35 (s, 6H), 1.78-1.95 (m, 4H), 3.0-3.11 (septet, J=6.8 Hz, 1H), 3.37-3.44 (q, J=4.97 Hz, 2H), 6.56, 7.38 (2d, J=7.6 Hz, 2H), 6.96 (s, 1H), 10.49 (s, 1H).

N-Formyl-2,3,4,5-Tetrahydro-9-isopropyl-10-methoxy-naphtho [6,5-*f*] azepine (*39*)

Amine *33* (0.62g, 2 mmol) was dissolved in THF (20 mL) and was followed by the addition of 98% HCOOH (1mL) and the solution was refluxed under nitrogen for 24 hours. Then water (50mL) was added and the solution was extracted with $CHCl_3$ (3X100mL). The organic extract was dried with $MgSO_4$, evaporated and purified by column chromatography (eluted with hexanes containing 25% EtOAc) to give compound *39* (0.5g, 72%). mp 143-144°C. MS: m/e (M^+) (calcd for $C_{21}H_{27}NO_2$: 325), (found: 325). ^{1}H-NMR (250MHz): δ 1.29 (d, J=6.85 Hz, 9H), 1.5 (s, 3H), 1.58-1.81 (m, 3H), 2.14-2.33 (m, 1H), 2.64-2.75 (m, 1H), 3.36-3.47 (septet, J=6.8 Hz, 1H), 3.91 (s, 3H), 4.76-4.82 (m, 1H), 6.98 (s, 1H), 7.43, 7.70 (2d, J=8.3 Hz, 2H), 8.15 (s,

1H). Anal. Calcd.: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.35; H, 8.60; N,3.95.

N-Formyl-2,3,4,5-Tetrahydro-9-isopropyl-naphtho[6,5- *f*]azepin-10-ol (*40*)

To a stirred solution of compound *39* (0.65g, 2 mmol) in CH_2Cl_2 (20mL) cooled at 0°C was added boron tribromide (0.7mL) slowly via a syringe. The solution was stirred at room temperature for 1 hour. Then ice water (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3X75mL). The organic layer was dried with $MgSO_4$, evaporated and purified by column chromatography (eluted with hexanes containing 35% EtOAc) to give compound *40* (0.47g, 76%) which was unstable. mp of compound *40* : 168-171°C. MS: m/e (M^+) (calcd for $C_{20}H_{25}NO_2$: 311), (found: 311). ^{1}H-NMR (250 MHz): δ 1.31-1.36 (m,9H) , 1.52 (s, 3H), 1.58-1.84 (m, 3H), 2.24-2.37 (m, 1H), 2.73-2.83 (m, 1H), 3.41-3.52 (m,1H), 4.75-4.80 (m, 1H), 7.24 (s, 1H), 7.38, 7.71 (2d, J=8.8 Hz, 1H), 7.63 (s, 1H), 8.19 (s, 1H), 9.98 (s, 1H).

N-Acetyl-2,3,4,5-Tetrahydro-9-isopropyl-10-methoxy-naphtho[6,5- *f*] azepine (*42*)

Compound *33* (0.15g, 0.5mol), KOH (1g), acetyl chloride (1mL) and toluene (10mL) was added into a 25mL round bottomed flask. The mixture was sonicated under nitrogen for 24 hours (bath temp. = 42°C). TLC showed that the reaction was incomplete and further reaction turned out to give no

improvement in terms of yield. Water (50mL) was added and the mixture was extracted with CH_2Cl_2 (3X100mL). The organic extract was dried with $MgSO_4$, evaporated and purified by column chromatography (eluted with hexanes containing 40% EtOAc) to give acetamide 42 (0.07g, 44%) and amine 33 (0.05g) was recovered. mp of *42*: 124-125°C; MS: m/e (M^+) (calcd for $C_{22}H_{29}NO_2$: 339.), (found: 339). ^{1}H-NMR (250 MHz): δ 1.05-1.2 (m, 9H), 1.40 (s, 3H), 1.45-1.75 (m, 6H), 2.2-2.35(m, 1H), 2.55-2.65 (m, 1H), 3.25-3.35 (septet, J=6.9 Hz, 1H), 3.85 (s, 3H), 4.7-4.8 (m, 1H), 6.8 (s, 1H), 7.3, 7.6 (2d, J=8.7 Hz, 2H), 7.5 (s, 1H). Anal. Calcd.: C, 77.84; H, 8.61; N, 4.13. Found : C, 77.14; H, 8.53; N, 3.81.

N-Acetyl-2,3,4,5-Tetrahydro-9-isopropyl-naphtho[6,5-*f*] azepin-10-ol (*43*)

To a stirred solution of compound *42* (0.58g, 1.7 mmole) in CH_2Cl_2 (20mL) cooled at 0°C was added boron tribromide (0.6mL) slowly via a syringe. The solution was stirred at room temperature for 1 hour. Then ice water (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3X75mL). The organic layer was dried with $MgSO_4$, evaporated and purified by column chromatography (eluted with hexanes containing 35% EtOAc) to give compound *43*(0.4g, 71%) which was unstable. mp 134-136°C. MS: m/e (M^+) (calcd for $C_{21}H_{27}NO_2$: 325), (found:325).. ^{1}H-NMR (250 MHz): 1.2-1.35 (m, 9H), 1.55 (s, 3H), 1.85 (s, 3H), 1.5-1.9 (m, 3H), 1.83 (s, 1H), 2.3-2.45 (m,1H), 2.7-2.8 (t, J=11 Hz, 1H), 3.40-3.96 (septet, J=6.9 Hz, 1H), 4.82-

4.87 (m, 1H), 7.23 (s, 1H), 7.36, 7.68 (2d, J=8.7 Hz, 2H), 7.62 (s, 1H), 10.74 (s, 1H).

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IX. List of Spectra

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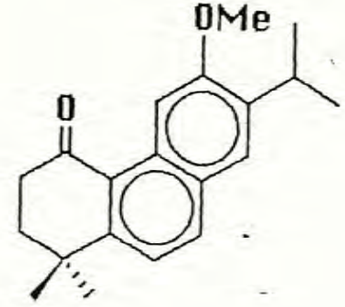


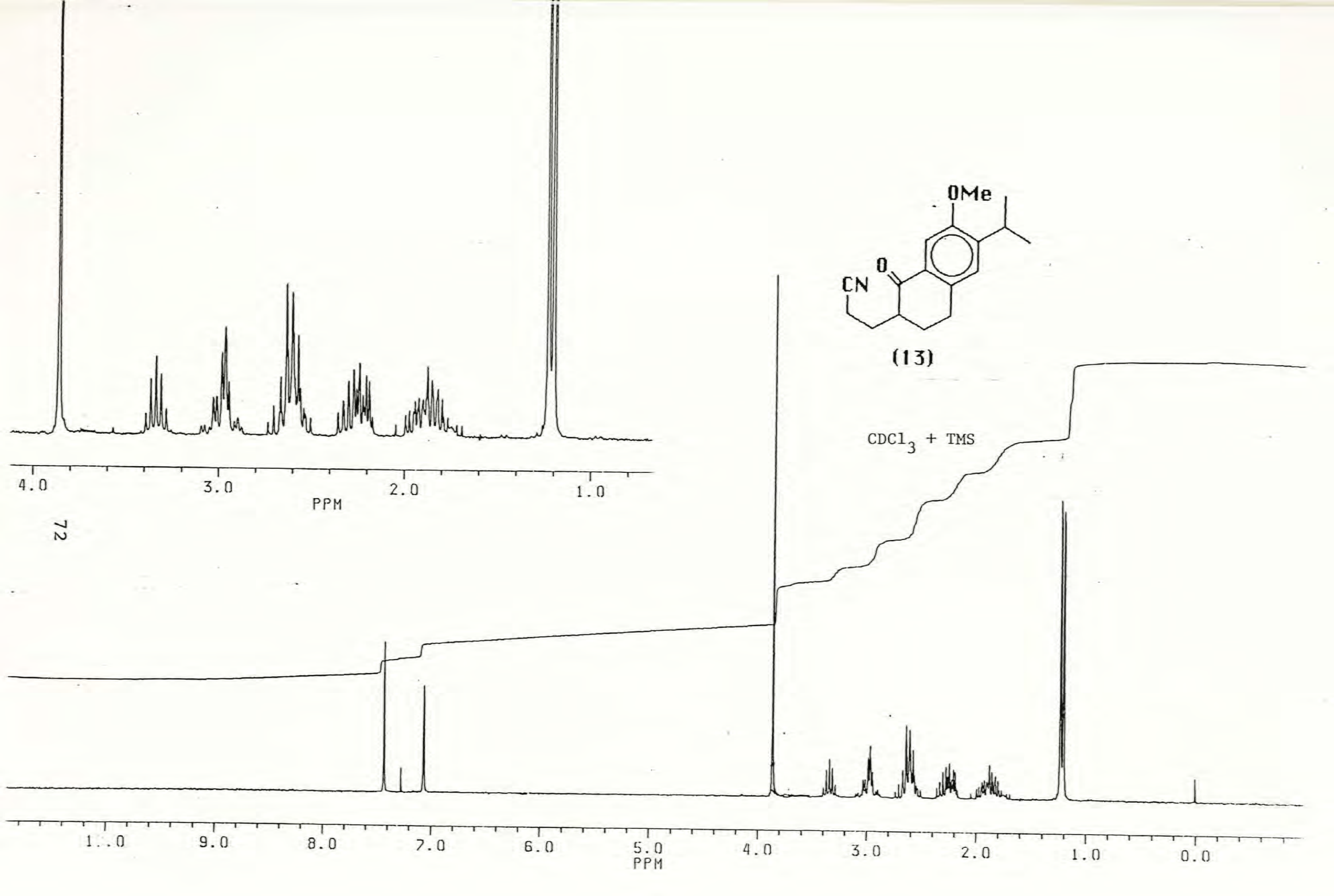
(11)

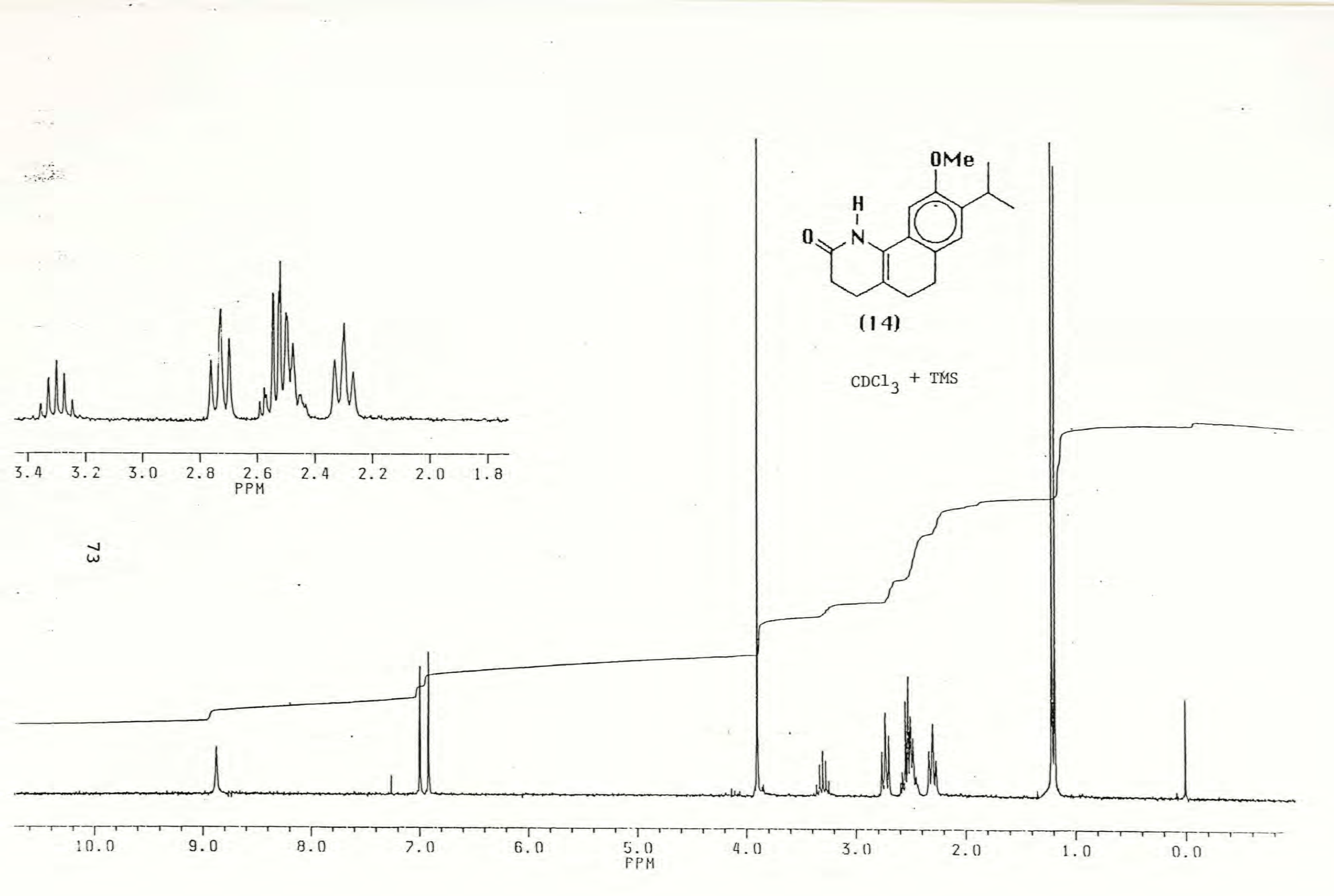
$CDCl_3$ + TMS

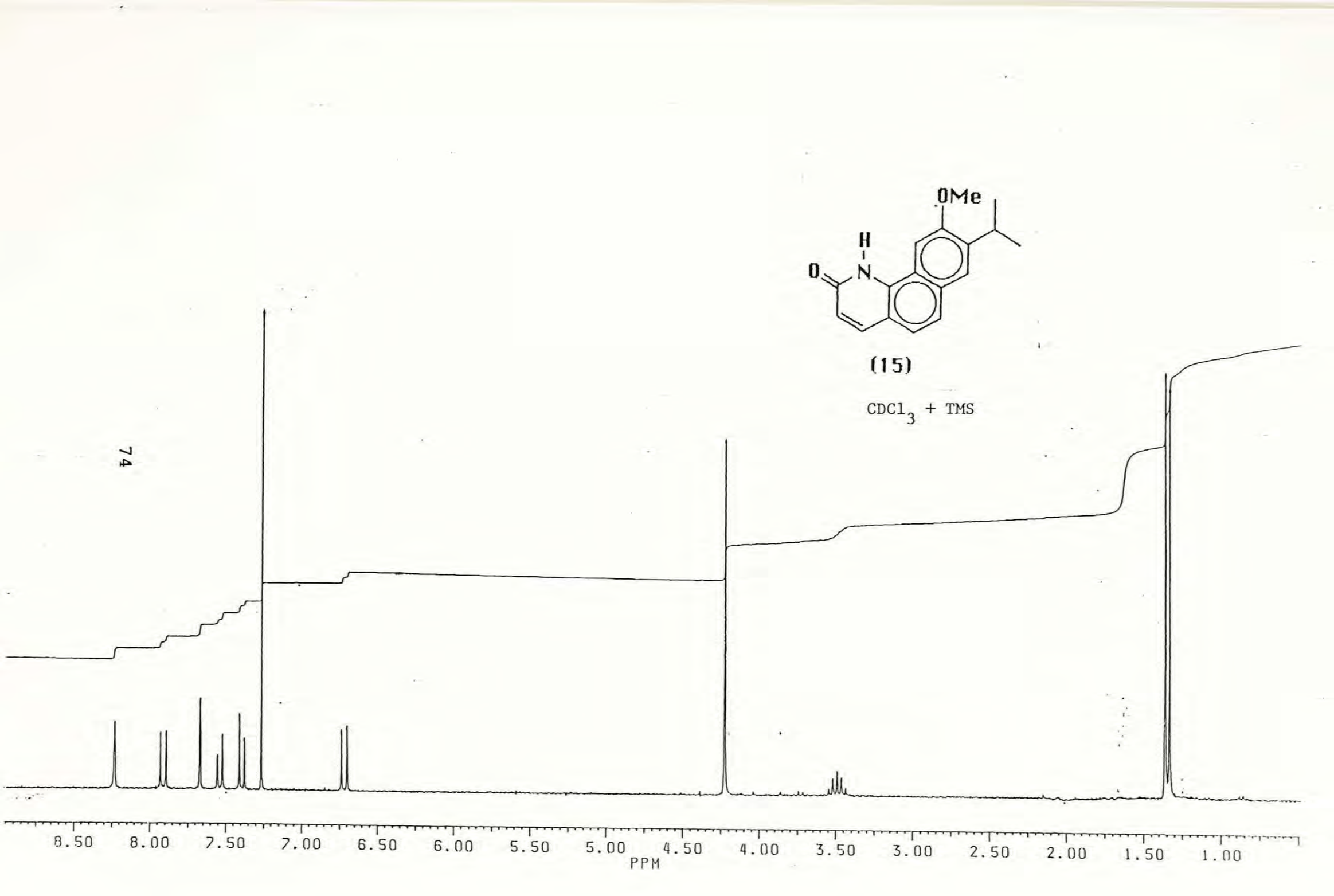
71

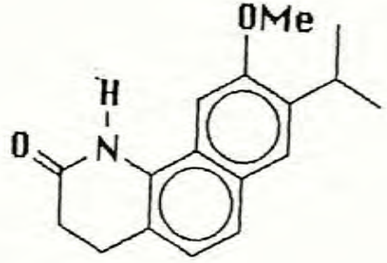
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0

PPM

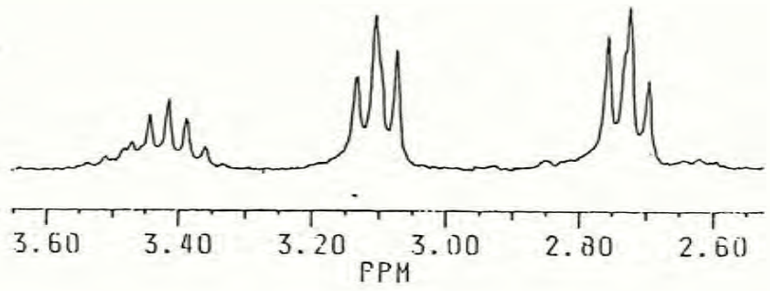

OMe
O
CN
(13)
CDCl3 + TMS
4.0
3.0
2.0
1.0
PPM
72
1..0
9.0
8.0
7.0
6.0
5.0
PPM
4.0
3.0
2.0
1.0
0.0


OMe
H
N
O
(14)
CDCl3 + TMS
3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8
PPM
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
PPM


OMe
H
N
O
(15)
CDCl3 + TMS
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
PPM

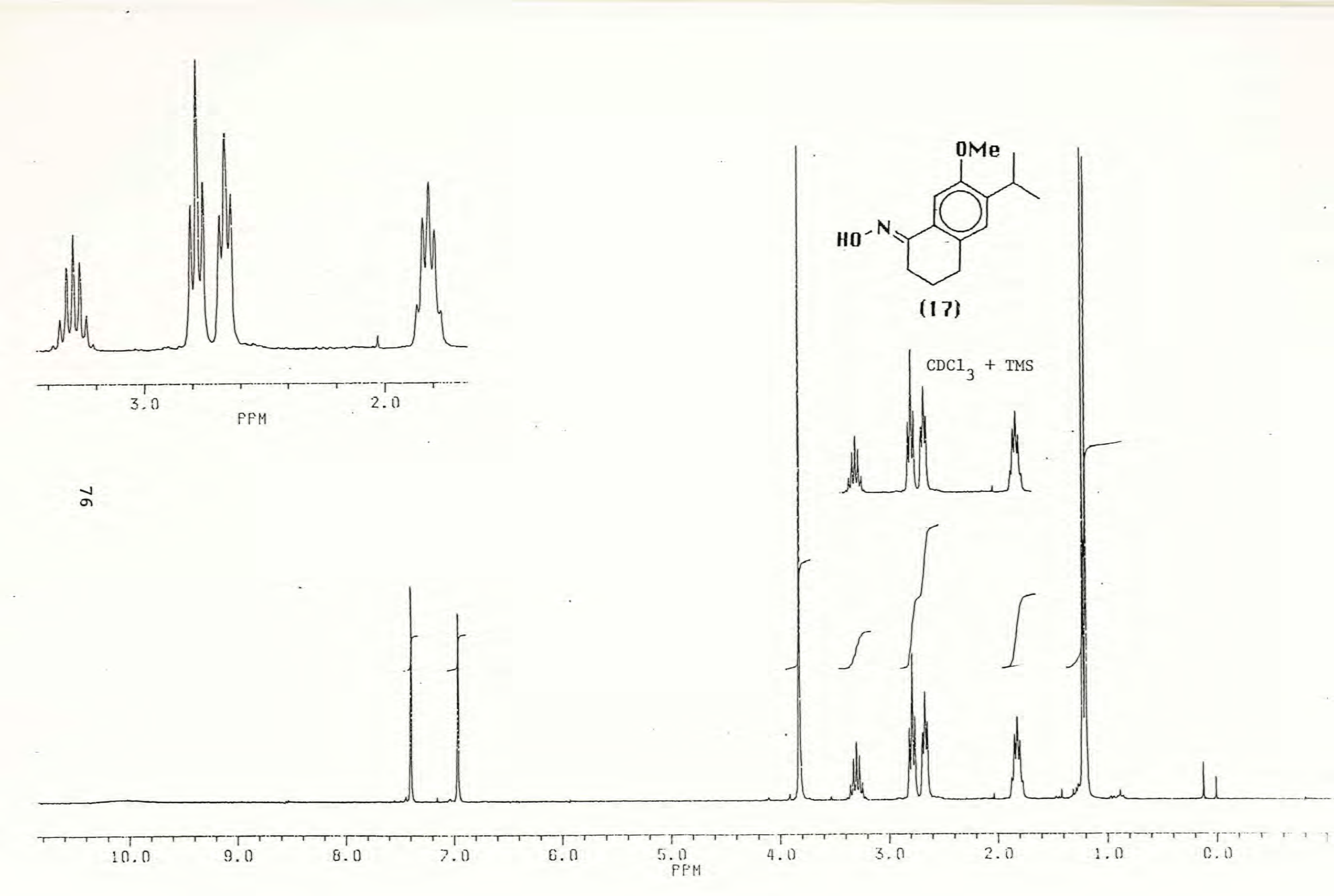


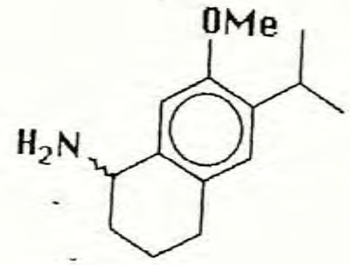
(16)



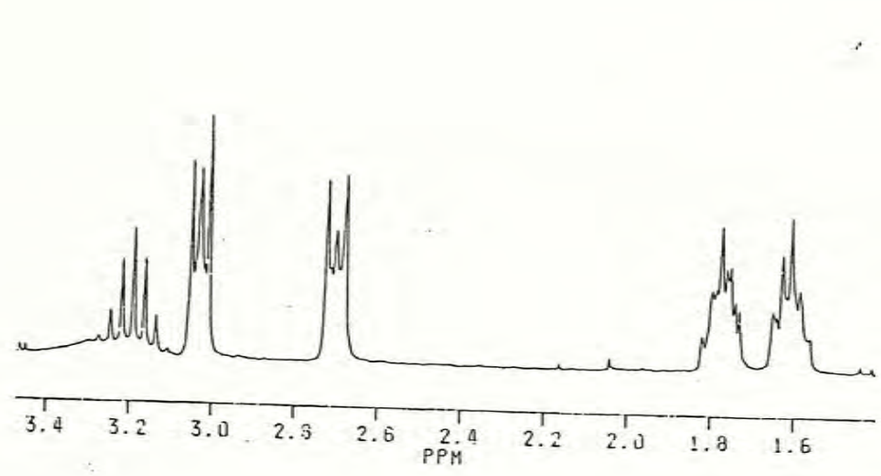
$CDCl_3$ + TMS

75

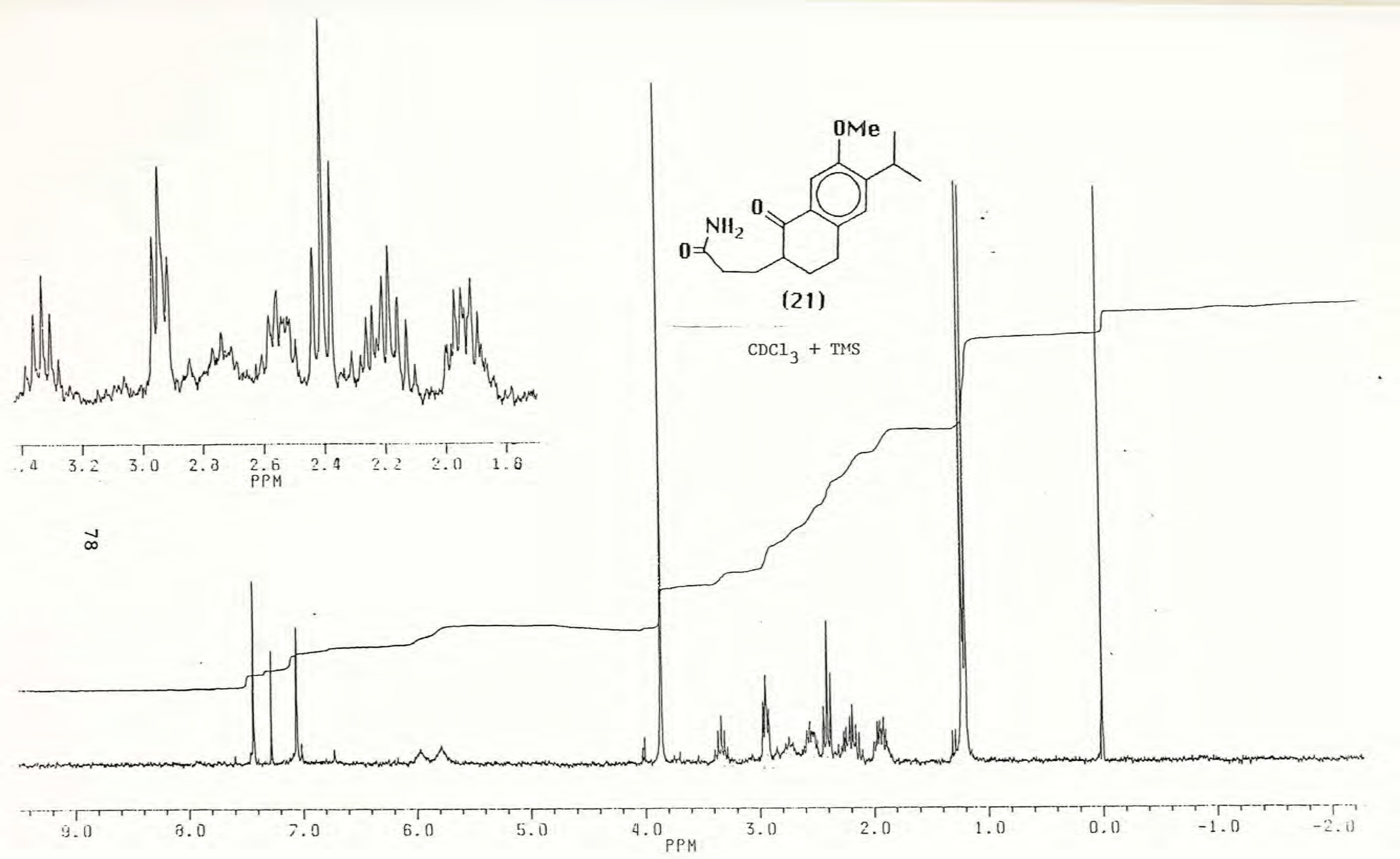

OMe
HO
N
(17)
CDCl3 + TMS
3.0
2.0
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

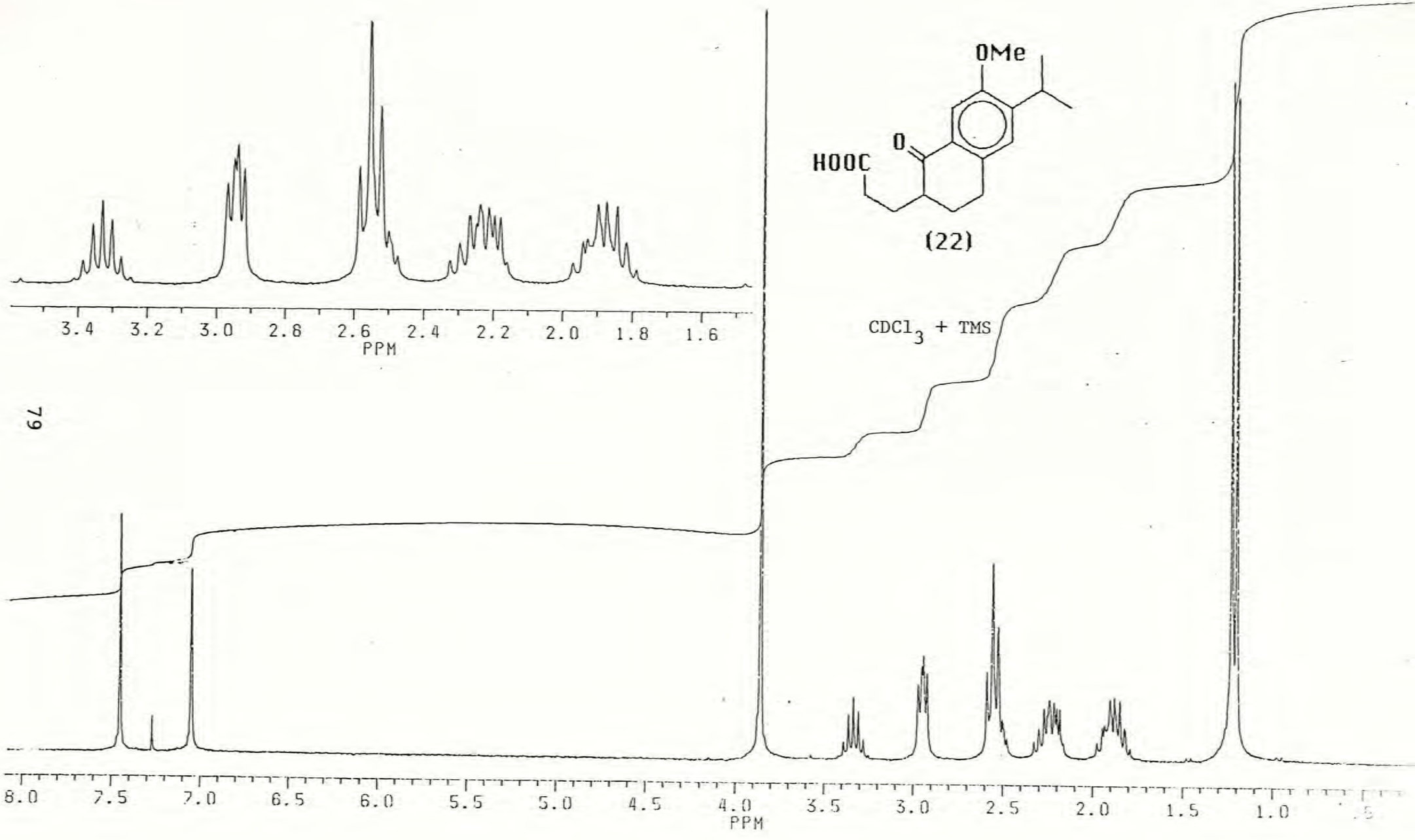

OMe
H_2N

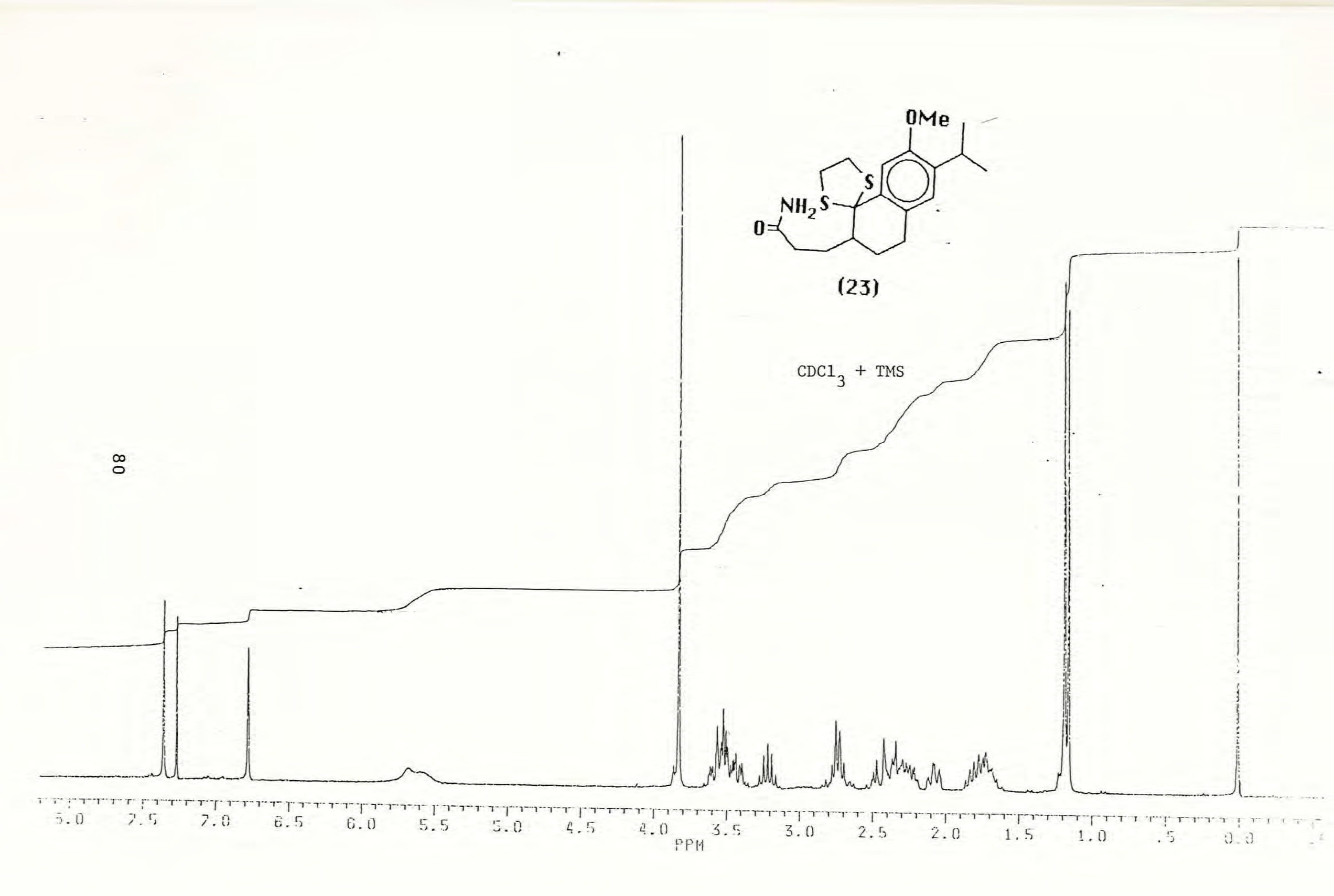
(18)

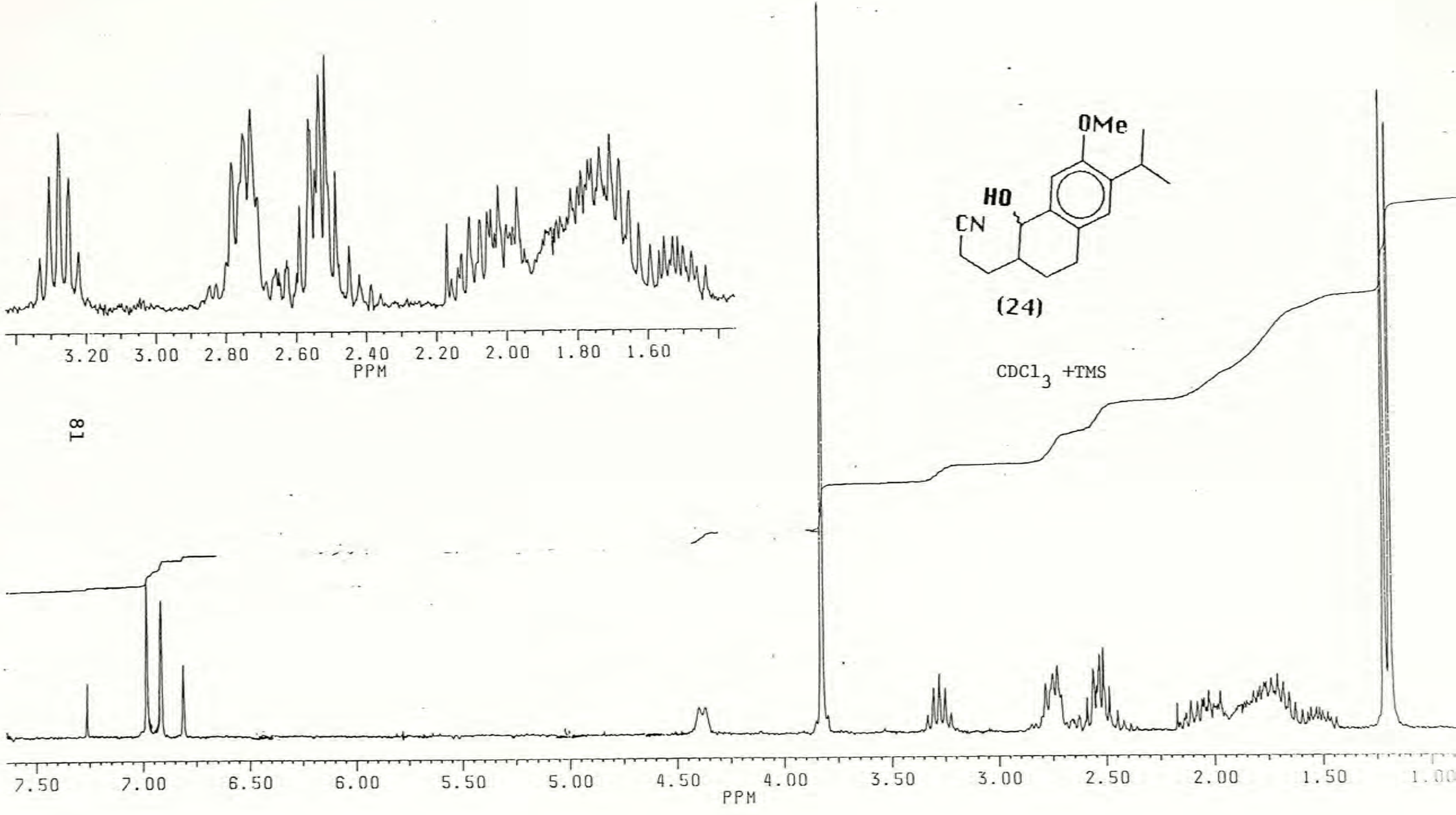

3.4
3.2
3.0
2.8
2.6
2.4
PPM
2.2
2.0
1.8
1.6

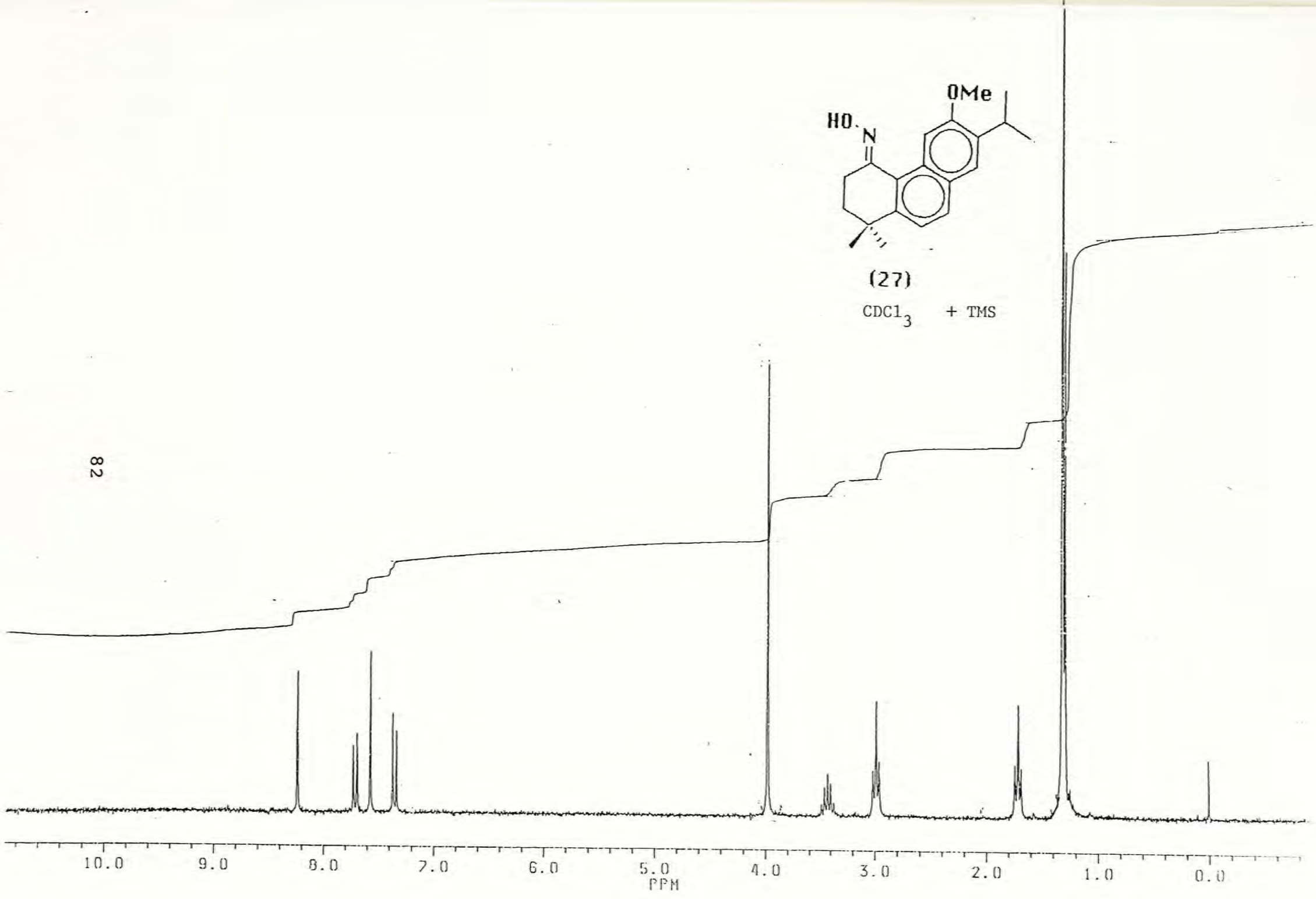
$CDCl_3$ + TMS
10.0
9.0
8.0
7.0
6.0
5.0
PPM
4.0
3.0
2.0
1.0
0.0

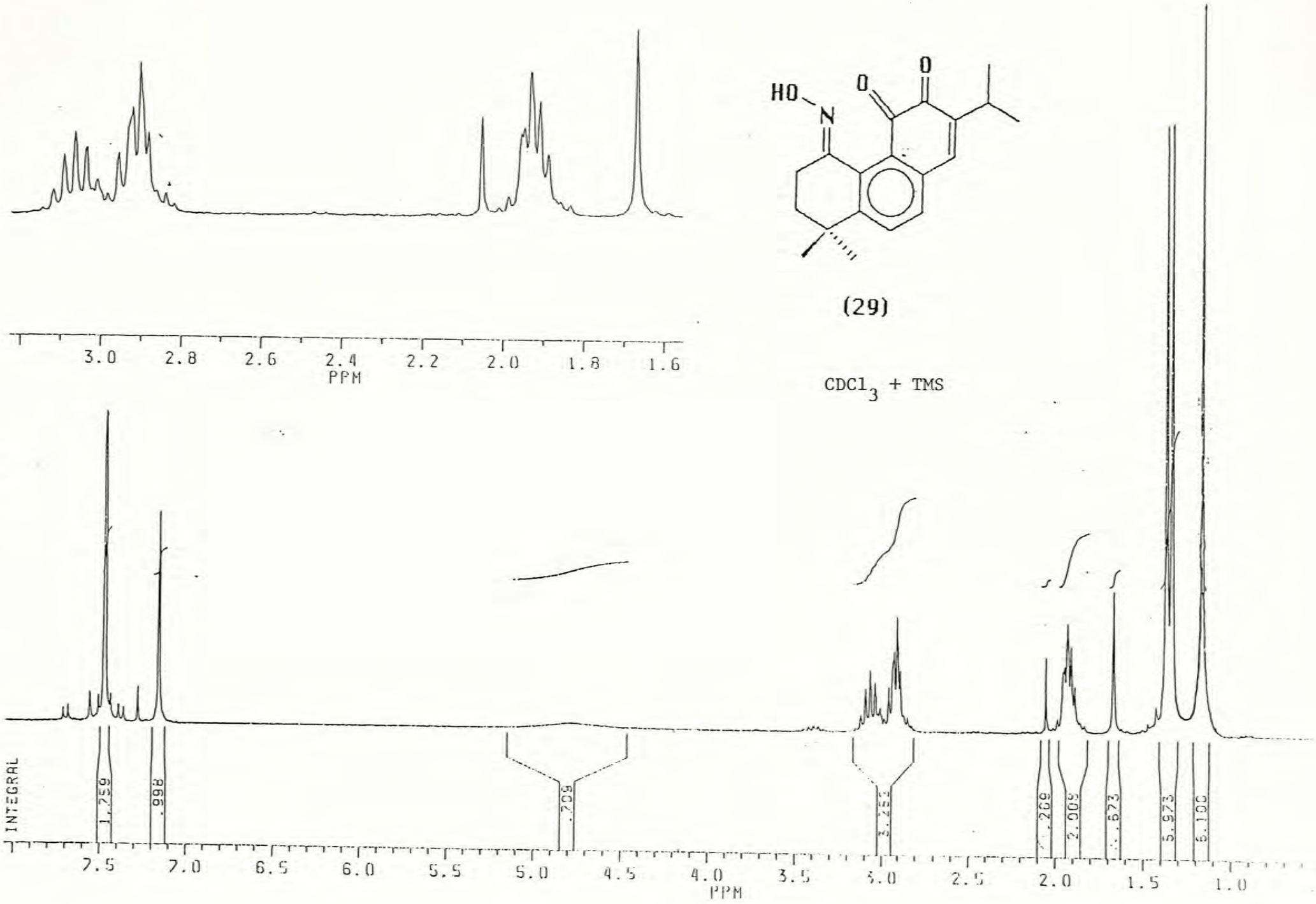

OMe
O
NH2
O
(21)
CDCl3 + TMS
3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8
PPM
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0 -1.0 -2.0
PPM

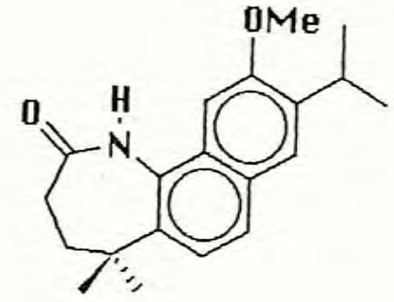

OMe
O
HOOC
(22)
CDCl3 + TMS
3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6
PPM
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
PPM


OMe
S
NH2 S
O
(23)
CDCl3 + TMS
80
5.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


OMe
HO
CN
(24)
CDCl3 +TMS
T8
3.20 3.00 2.80 2.60 2.40 2.20 2.00 1.80 1.60
PPM
7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00
PPM


OMe
HO
N
(27)
CDCl3 + TMS
82
10.0
9.0
8.0
7.0
6.0
5.0
PPM
4.0
3.0
2.0
1.0
0.0


HO
N
O
O
(29)
CDCl3 + TMS
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
PPM
INTEGRAL
1.259
.998
.709
3.455
.269
2.909
.673
5.973
6.106
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
PPM

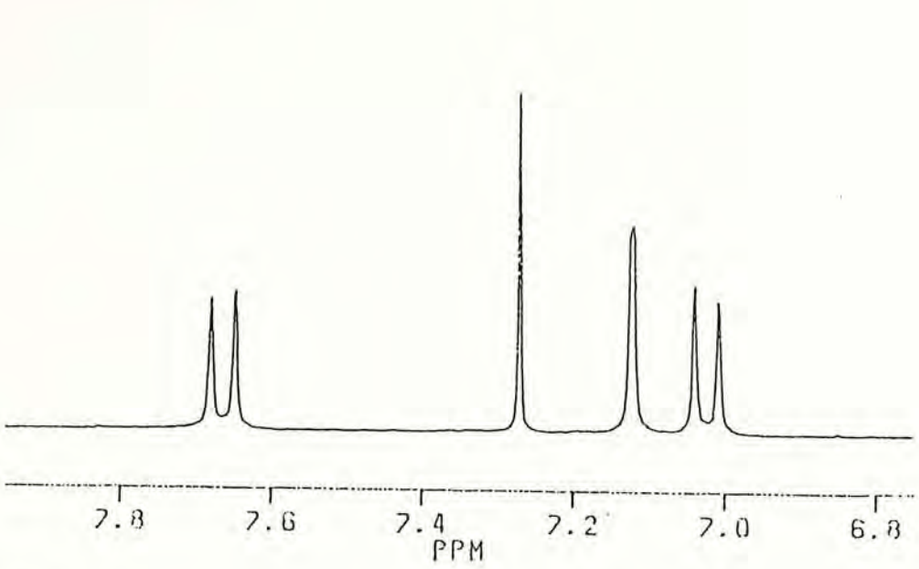


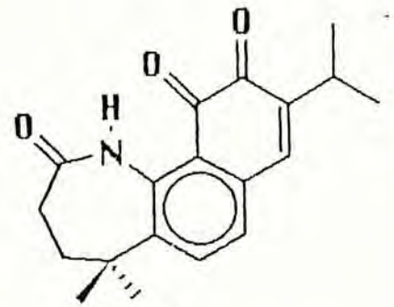
(30)

$CDCl_3$ + TMS

10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0

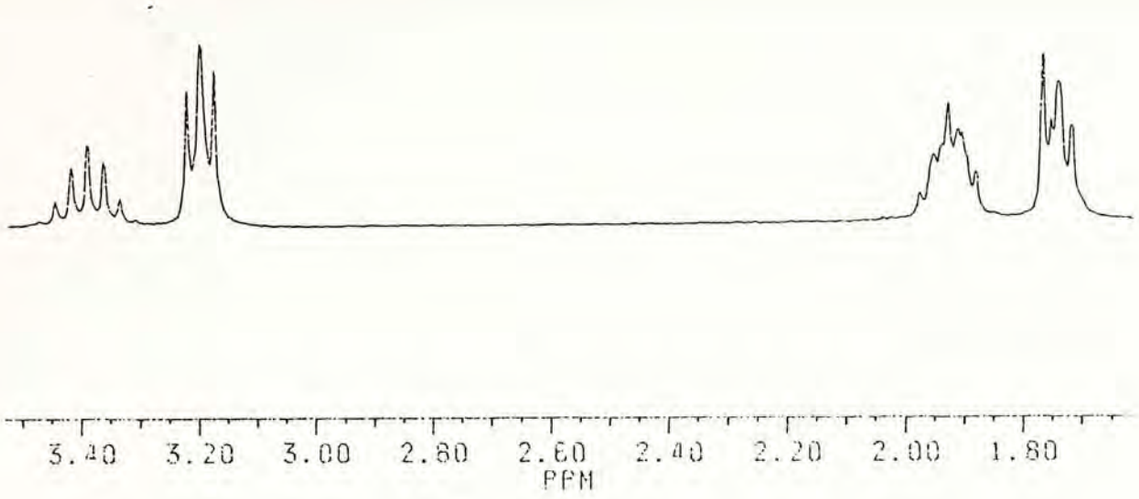
PPM

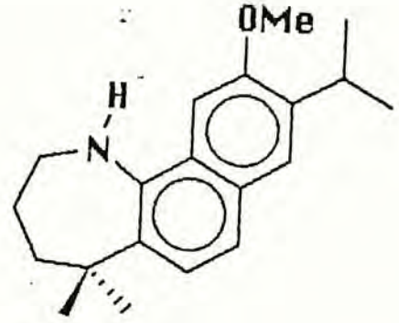




(32)

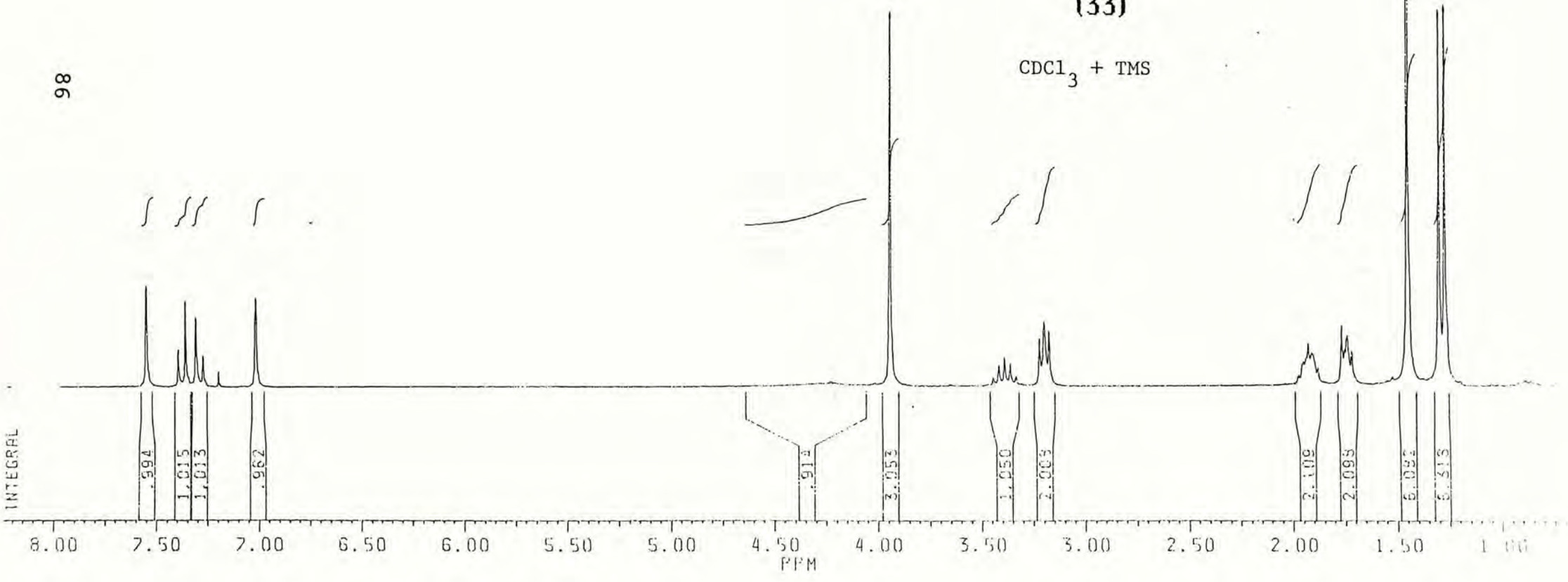
$CDCl_3$ + TMS

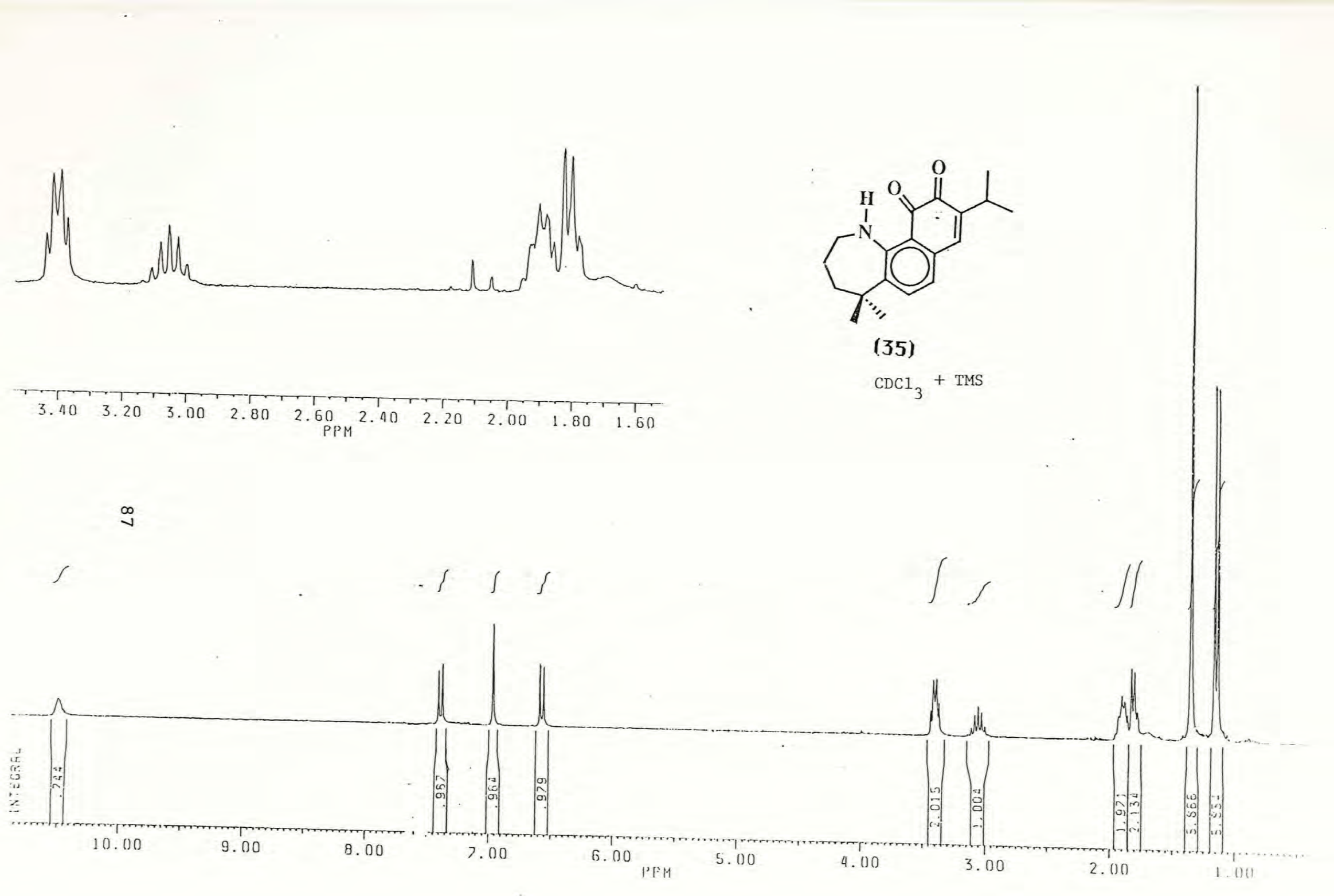

3.40
3.20
3.00
2.80
2.60
2.40
2.20
2.00
1.80
PPM

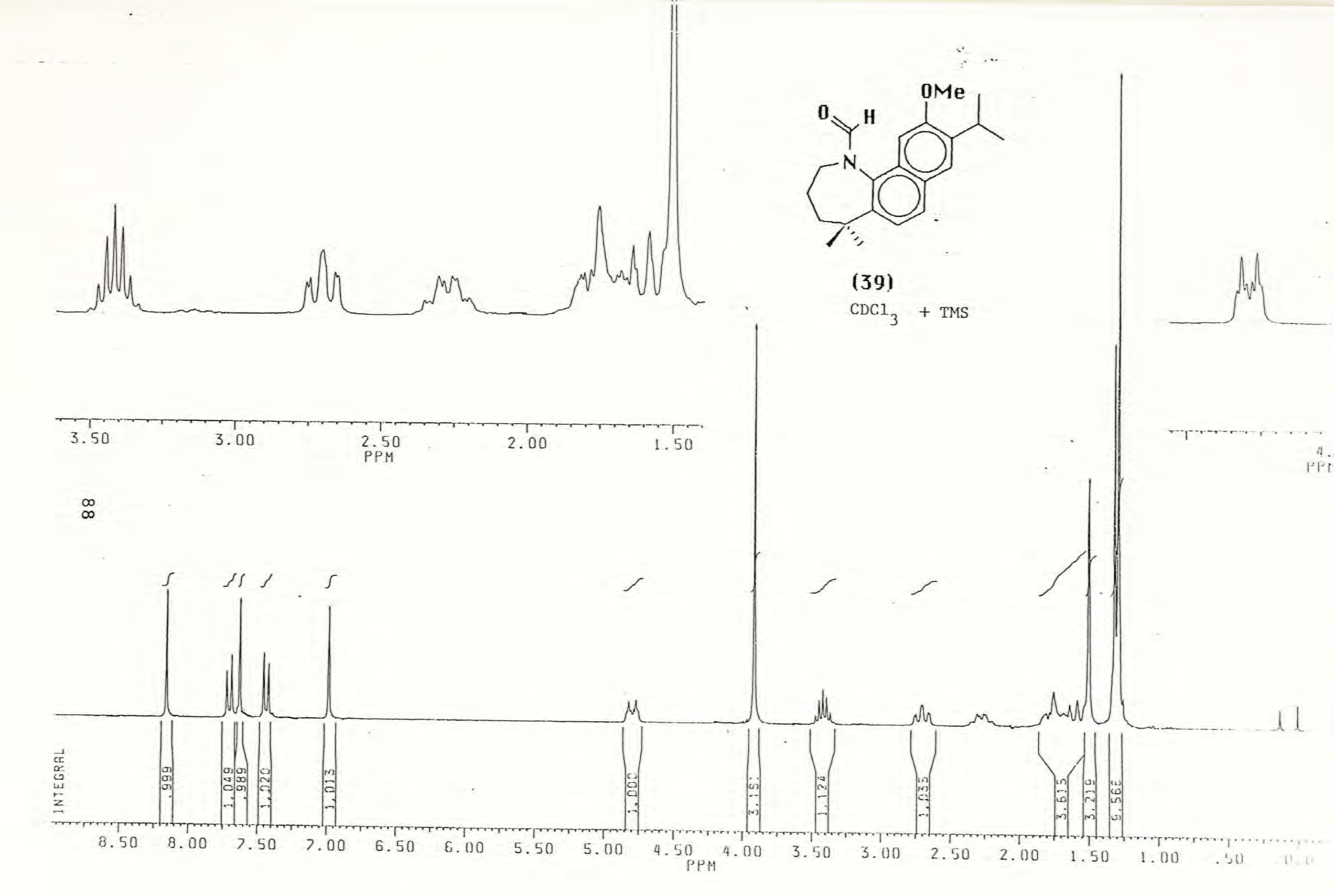

OMe
H
N

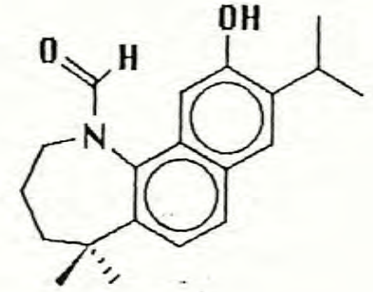
(33)

$CDCl_3$ + TMS


INTEGRAL
.594
1.015
1.013
.962
.914
3.053
1.050
2.003
2.108
2.093
6.082
6.316
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
PPM

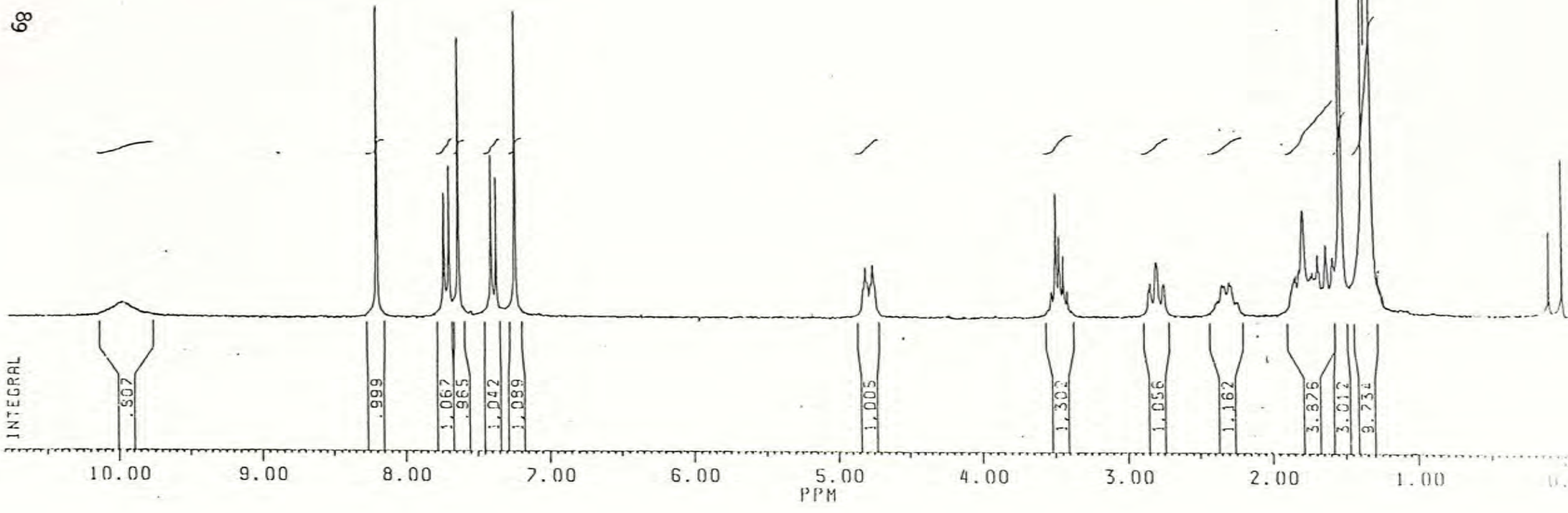

O
O
H
N
(35)
CDCl3 + TMS
87
3.40 3.20 3.00 2.80 2.60 2.40 2.20 2.00 1.80 1.60
PPM
INTEGRAL
.244
.957
.964
.979
2.015
1.004
1.971
2.134
3.866
5.954
10.00 9.00 8.00 7.00 6.00 5.00 4.00 3.00 2.00 1.00
PPM

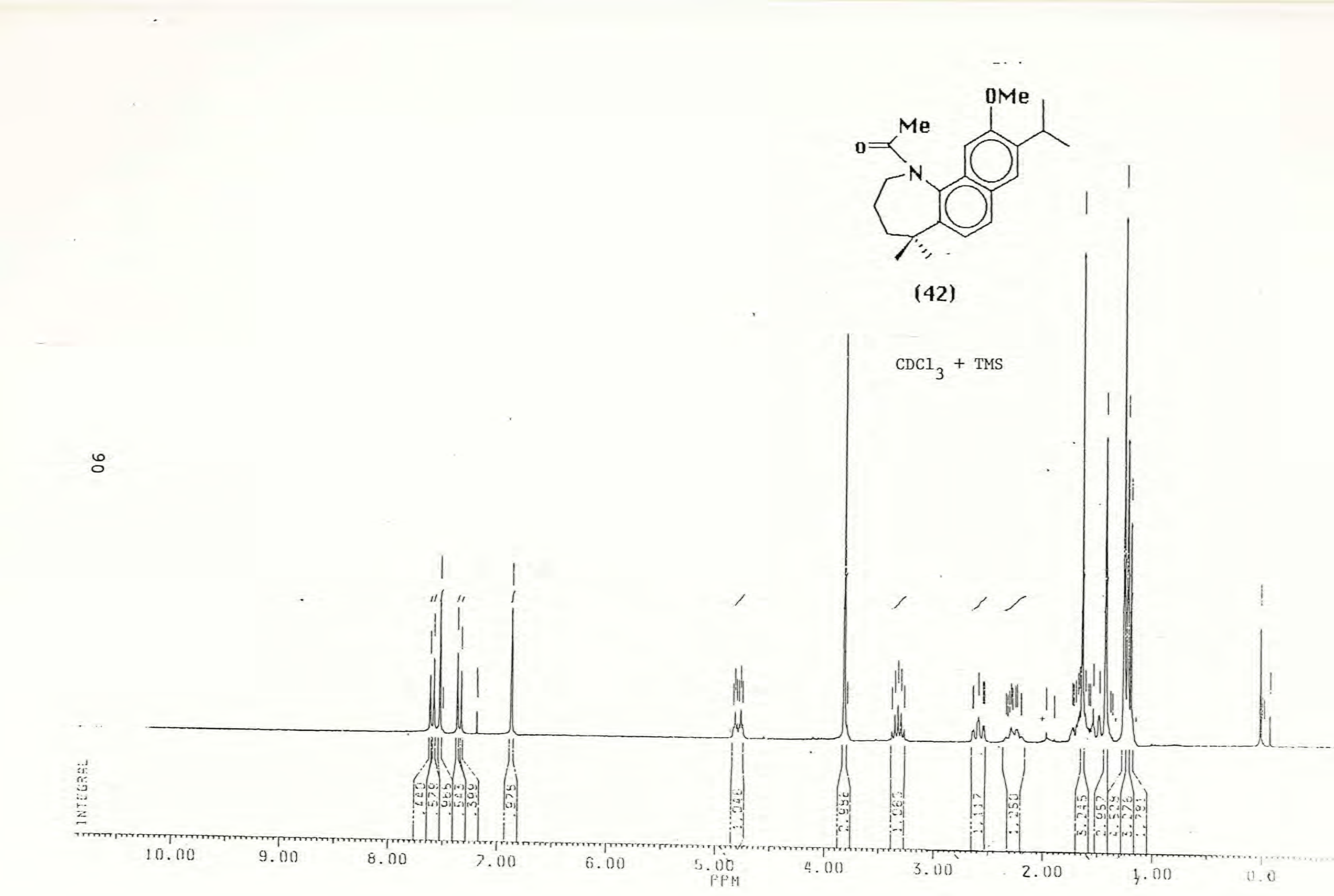

OMe
O
H
N
(39)
CDCl3 + TMS
88
INTEGRAL
.999
1.049
.989
1.020
1.013
1.000
3.157
1.124
1.035
3.615
3.219
3.568
PPM

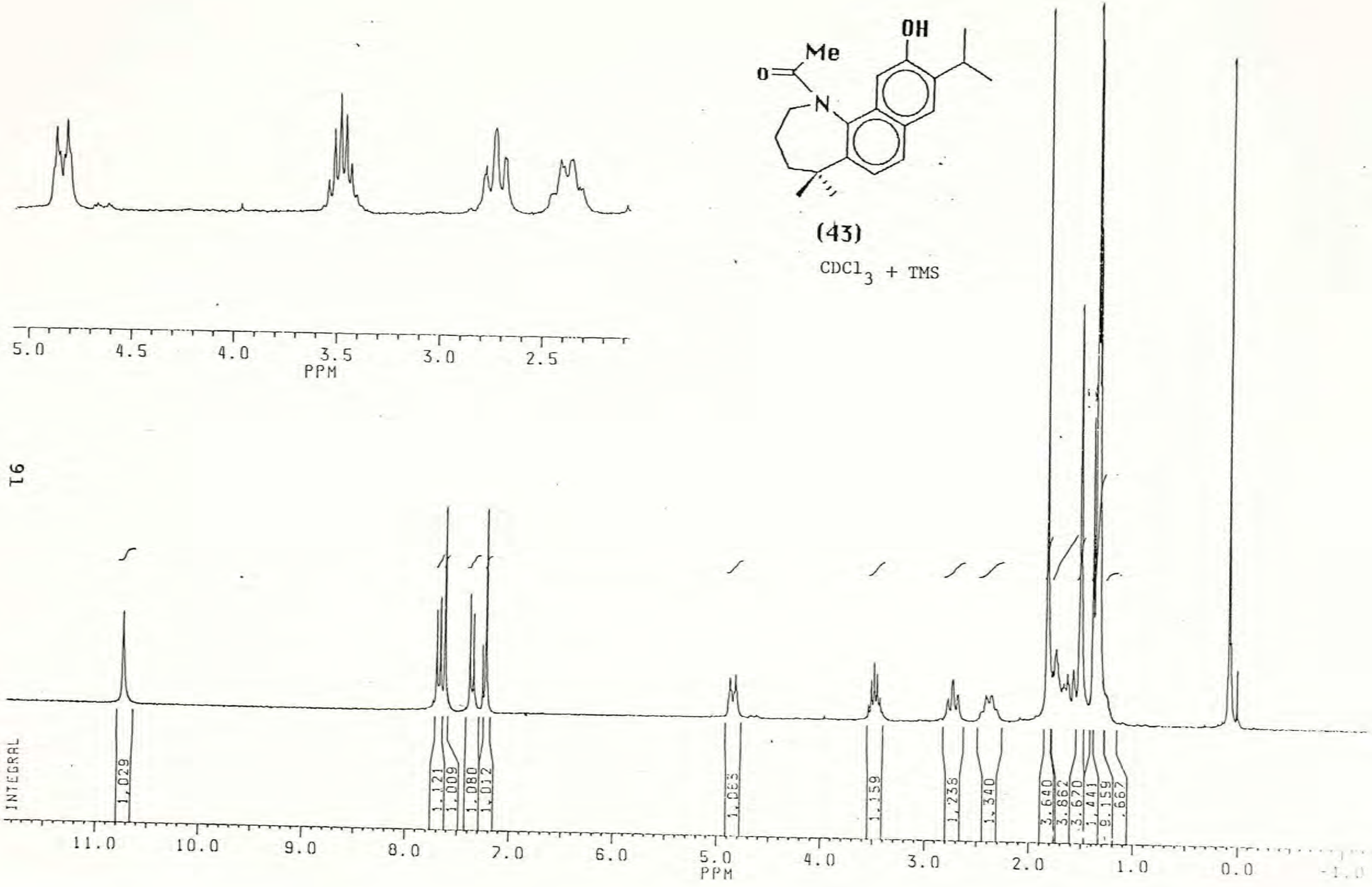

OH
O
H
N

(40)

$CDCl_3$ + TMS


INTEGRAL
.807
.999
1.062
.965
1.042
1.089
1.005
1.302
1.056
1.162
3.826
3.012
3.734
10.00
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
PPM


OMe
Me
O
N
(42)
CDCl3 + TMS
06
INTEGRAL
10.00
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.0
PPM


OH
Me
O
N
5.0
4.5
4.0
3.5
3.0
2.5
PPM
INTEGRAL
1.029
1.121
1.009
1.080
1.012
1.083
1.159
1.236
1.340
3.640
3.862
3.670
1.441
9.159
.667
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

(43)

$CDCl_3$ + TMS